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Advances in the care of the pediatric pulmonary hypertension patient: From the neonate to the adolescent-young adult patient

Edited by
Catherine Avitabile, Rachel Hopper, Stephanie Handler and Angela Bates

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Advances in the care of the pediatric pulmonary hypertension patient: From the neonate to the adolescent-young adult patient

Topic editors

Catherine Avitabile — Children's Hospital of Philadelphia, United States
Rachel Hopper — Stanford University, United States
Stephanie Handler — Medical College of Wisconsin, United States
Angela Bates — University of Alberta, Canada

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Ruth Heying,
University Hospital Leuven, Belgium

*CORRESPONDENCE
Catherine M. Avitabile
✉ avitabilec@chop.edu

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Editorial: Advances in the care of the pediatric pulmonary hypertension patient: from the neonate to the adolescent-young adult patient

Catherine M. Avitabile[1]*, Rachel K. Hopper[2], Stephanie S. Handler[3] and Angela Bates[4]

[1]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [2]Department of Pediatrics, Stanford University School of Medicine, Division of Cardiology, Lucile Packard Children's Hospital, Palo Alto, CA, United States, [3]Department of Pediatrics, Medical College of Wisconsin, Division of Cardiology, Children's Hospital of Wisconsin, Madison, WI, United States, [4]Department of Pediatrics, University of Alberta, Division of Cardiology Stollery Children's Hospital, Edmonton, AB, Canada

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Editorial on the Research Topic
Advances in the care of the pediatric pulmonary hypertension patient: from the neonate to the adolescent-young adult patient

In pediatric pulmonary hypertension (PH), occlusion of small pulmonary arteries leads to increased right ventricular afterload and risk of right heart failure. In recent years, therapeutic options have increased for young patients, however, in the United States most treatments are given "off-label" without formal approval from the Food & Drug Administration. Despite treatment advances, PH remains a life-altering and life-limiting diagnosis for many infants and children. This Research Topic presents novel approaches to the diagnosis, treatment, and risk assessment of PH across the pediatric spectrum. Contributions address novel medical and transcatheter interventions, multidisciplinary care, and risk scoring in pediatric PH. The collection of manuscripts increases awareness of the complexity of this disease and advances the goal of improving functional status, quality of life, and survival in children with this serious condition.

Several manuscripts present critically important pediatric experience with off-label pulmonary vasodilator therapies. Tadalafil is a once-daily, long-acting phosphodiesterase type 5 inhibitor with a favorable side effect profile but limited data in children. Youssef and colleagues describe improvement in right ventricular function and minimal side effects in 154 children treated with tadalafil suspension (both *de novo* and transition cases) at two North American centers. These encouraging data are especially relevant in young children with PH who cannot tolerate enteral tablets due to age, developmental status, or feeding tube requirements. Domingo and colleagues describe novel use of riociguat, an oral soluble guanylate cyclase stimulator, in 2 infants with genetic mutations and severe, nitric oxide-dependent pulmonary arterial hypertension who did not respond to sildenafil. This experience should prompt further study of riociguat, especially in neonatal populations with respiratory failure and high utilization of nitric oxide, in order to expand therapeutic options in the sickest children. Three manuscripts add to knowledge about selexipag, an

oral selective prostacyclin receptor agonist, with clear benefits in adult PH but limited published experience in pediatric PH. In a case report, Hasan and colleagues describe a neonate with developmental lung disease related-PH refractory to phosphodiesterase type 5 inhibitor and endothelin receptor antagonist treatment who demonstrated clinical and echocardiographic improvement with selexipag. In a second manuscript, Youssef's group describes a heterogeneous group of 24 PH patients treated with selexipag at 3 Canadian centers. In short term follow-up (12 months), most patients maintained clinical stability with expected gastrointestinal side effects. Faircloth and colleagues describe their experience initiating, transitioning, and titrating selexipag in 7 children (2 *de novo*, 5 transition from continuous prostacyclin) younger than 10 years of age with weights 10–30 kg. Their institution-specific algorithm provides practical insight for other centers and supports continued successful use in the pediatric population. These studies also highlight the reliance of pediatric PH treatment on case reports and observational studies given the challenges of performing randomized clinical trials in children. However, continued observational work and novel trial designs are critical to test pulmonary vasodilator therapies in the pediatric population and increase access to medications traditionally limited to adult use.

Two manuscripts describe innovative transcatheter interventions to treat pediatric PH. Closure of an atrial septal defect can be a challenging decision in pediatric PH, particularly in those with Group 3 lung disease related-PH as providers may weigh the benefit of alleviating arterial damage from left-to-right intracardiac shunt against the loss of the right-to-left "pop off" during times of acute RV failure or low cardiac output. In a third manuscript, Youssef and colleagues report a single-center, Canadian experience with atrial flow regulators and fenestrated atrial septal defect occluders, allowing controlled closure of these defects with some degree of right-to-left shunt if needed. The data suggests Group 1 patients may demonstrate clinical improvement with this innovative approach, and future multicenter studies should identify ideal pediatric candidates and optimal intervention timing. Additionally, Haddad and colleagues describe their experience with transcatheter Potts shunt creation in children with severe pulmonary arterial hypertension. The reverse Potts shunt creates or maintains a connection between the pulmonary artery and aorta, allowing right to left interarterial shunting and prevention of right ventricular failure at the expense of lower extremity cyanosis. In Haddad's report, 13 patients underwent endovascular stenting of a patent arterial ducts or aorta-to-pulmonary radiofrequency perforation and covered stent placement. At median follow-up of 77 months, patients demonstrated improvement in functional class and high 6-year survival (92.3%) with frequent transcatheter re-intervention on the graft or stent. These data further inform our understanding of the longer-term outcomes of this palliative alternative for patients with severe PH and exhaustion of treatment options other than lung transplantation.

The breadth and complexity of pediatric PH is highlighted in several manuscripts detailing a need for comprehensive, multidisciplinary care in this population. Yung and colleagues outline their center-specific, systematic approach to care of infants with bronchopulmonary dysplasia related-PH (BPD-PH). With optimization of respiratory support, low threshold for closure of intracardiac and interarterial shunts, and initiation of pulmonary vasodilators only after diagnostic confirmation by cardiac catheterization, they report universal resolution of PH. In particular, these findings emphasize the need to consider the impact of shunts in patients with developmental lung diseases and limited pulmonary vascular beds. Sullivan and colleagues also augment the understanding of BPD-PH through their description of cardiac catheterization data from 34 patients with BPD, 32% of whom had left atrial hypertension defined as a pulmonary capillary wedge pressure >10 mm Hg. Left atrial hypertension was associated with increased risk of tracheostomy and/or death, suggesting that left atrial hypertension (from left ventricular diastolic dysfunction or intracardiac shunts) may play a role in pathogenesis and patient outcomes.

Comprehensive pediatric PH care requires many subspecialists including geneticists, nutritionists, laboratory medicine specialists, rehabilitation teams, and other experts. Ishizuka and colleagues report the burden of heritable pulmonary arterial hypertension at a large PH referral center. Among 66 patients who underwent genetic testing, 14% were found to have a pathogenic mutation, most commonly BMPR2 mutations, with severe hemodynamic findings. These "real-world" single-center clinical data support larger scale population studies to characterize the burden of heritable pulmonary arterial hypertension in the pediatric population in order to develop targeted treatment approaches. Ruland and colleagues demonstrate that malnutrition is underappreciated and underdiagnosed in pediatric PH but that treatment by a registered dietitian improves malnutrition status in many patients at their center. The need for close monitoring and individualized nutrition recommendations can be delivered through a multidisciplinary team at a comprehensive pediatric PH center. Wieland and colleagues report acquired von Willebrand syndrome with bleeding complications in a series of patients with severe PH requiring bilateral lung transplantation, highlighting the importance of considering this diagnosis in patients undergoing surgical interventions or experiencing trauma. Avitabile and colleagues reported associations between skeletal muscle deficits and worse exercise performance on cardiopulmonary exercise testing and exercise cardiac magnetic resonance imaging in adolescents with PH. These data may support interventions to improve muscle mass and strength as a potential means to improve functional status and quality of life in this population.

Finally, Lokhorst and colleagues present a systematic review of risk stratification in adult and pediatric PH, which is critical to determining treatment strategy. They identified the most common variables in risk stratification models as: World Health Organization functional class, 6-minute walk test distance, N-terminal pro brain natriuretic peptide level, and mean right atrial pressure, cardiac index, and mixed venous oxygen saturation on cardiac catheterization; however, they identified very limited data on risk stratification in pediatric PH. Future studies must test these adult-focused scoring systems in large pediatric PH registry populations and identify new pediatric-specific imaging parameters, serum biomarkers, and physical activity metrics that predict mortality in children.

In conclusion, this Research Topic presents important advances in pediatric PH, but we are reminded that much work remains to be done. This collection provides a framework for identifying future areas of research for pediatricians, advanced practice providers, and PH providers who share the common goal of advancing the care of this vulnerable population from the neonatal period to adolescent-young adulthood.

We are grateful to the many pediatric PH experts who contributed their science to this Research Topic collection and to the peer reviewers and editors who provided critical feedback which further improved the quality of the publications.

Author contributions

CMA crafted the manuscript. RKH, SSH, and AB edited and revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Benjamin Frank,
University of Colorado, United States

REVIEWED BY
Jeffrey Fineman,
University of California, San Francisco, United States
Patrick D. Evers,
Oregon Health and Science University, United States

*CORRESPONDENCE
Rachel T. Sullivan
rachel.t.sullivan@vumc.org

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Role of left atrial hypertension in pulmonary hypertension associated with bronchopulmonary dysplasia

Rachel T. Sullivan[1]*, Megha D. Tandel[2], Shazia Bhombal[3], Gregory T. Adamson[4], Derek B. Boothroyd[2], Michael Tracy[5], Amanda Moy[3] and Rachel K. Hopper[4]

[1]Division of Pediatric Cardiology, Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN, United States, [2]Quantitative Sciences Unit, Department of Medicine, School of Medicine, Stanford University, Palo Alto, CA, United States, [3]Division of Neonatal and Developmental Medicine, Department of Pediatrics, School of Medicine, Stanford University, Palo Alto, CA, United States, [4]Division of Pediatric Cardiology, Department of Pediatrics, School of Medicine, Stanford University, Palo Alto, CA, United States, [5]Division of Pulmonary Medicine, Department of Pediatrics, School of Medicine, Stanford University, Palo Alto, CA, United States

Left atrial hypertension (LAH) may contribute to pulmonary hypertension (PH) in premature infants with bronchopulmonary dysplasia (BPD). Primary causes of LAH in infants with BPD include left ventricular diastolic dysfunction or hemodynamically significant left to right shunt. The incidence of LAH, which is definitively diagnosed by cardiac catheterization, and its contribution to PH is unknown in patients with BPD-PH. We report the prevalence of LAH in an institutional cohort with BPD-PH with careful examination of hemodynamic contributors and impact on patient outcomes. This single-center, retrospective cohort study examined children <2 years of age with BPD-PH who underwent cardiac catheterization at Lucile Packard Children's Hospital Stanford. Patients with unrepaired simple shunt congenital heart disease (CHD) and pulmonary vein stenosis (only 1 or 2 vessel disease) were included. Patients with complex CHD were excluded. From April 2010 to December 2021, 34 patients with BPD-PH underwent cardiac catheterization. We define LAH as pulmonary capillary wedge pressure (PCWP) or left atrial pressure (LAP) of at least 10 mmHg. In this cohort, median PCWP was 8 mmHg, with LAH present in 32% (n = 11) of the total cohort. A majority (88%, n = 30) of the cohort had severe BPD. Most patients had some form of underlying CHD and/or pulmonary vein stenosis: 62% (n = 21) with an atrial septal defect or patent foramen ovale, 62% (n = 21) with patent ductus arteriosus, 12% (n = 4) with ventricular septal defect, and 12% (n = 4) with pulmonary vein stenosis. Using an unadjusted logistic regression model, baseline requirement for positive pressure ventilation at time of cardiac catheterization was associated with increased risk for LAH (odds ratio 8.44, 95% CI 1.46–48.85, p = 0.02). Small for gestational age birthweight, sildenafil use, and CHD were not associated with increased risk for LAH. LAH was associated with increased risk for the composite outcome of tracheostomy and/or death, with a hazard ratio of 6.32 (95% CI 1.72, 22.96; p = 0.005). While the etiology

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of BPD-PH is multifactorial, LAH is associated with PH in some cases and may play a role in clinical management and patient outcomes.

KEYWORDS

left atrial hypertension, pulmonary hypertension, bronchopulmonary dysplasia (BPD), prematurity, diastolic dysfunction

Introduction

Premature infants with bronchopulmonary dysplasia (BPD), or chronic lung disease of prematurity, are at risk for developing pulmonary vascular disease and associated pulmonary hypertension (PH). PH is defined hemodynamically by a mean pulmonary artery pressure (PAP) >20 mmHg (1). Approximately 20% of infants with BPD develop PH, and this risk increases with BPD severity (2–6). Immature alveolar and pulmonary vascular development, in combination with complex postnatal factors, results in decreased pulmonary vascular surface area, altered vascular tone, and pathologic vascular changes that culminate in PH (7–9). While lung disease is a main driver of pulmonary vascular disease in premature infants, there is increasing concern about the potential contribution of left atrial hypertension (LAH), which may result from left ventricular diastolic dysfunction or a volume load from a hemodynamically significant left to right shunt (10). LAH may have important clinical implications in the management of BPD-PH, as the use of pulmonary vasodilator therapy in the setting of unrecognized LAH may promote pulmonary edema and result in worsened respiratory status and/or prolonged need for respiratory support. Mourani et al. reported two cases of infants with BPD-PH in whom LAH was present at cardiac catheterization and thought to contribute to both pulmonary hypertension and significant diuretic-dependent pulmonary edema (11).

The incidence of LAH, which is definitively diagnosed by cardiac catheterization, and its contribution to BPD-PH is unknown. Some groups have explored the ability to identify diastolic dysfunction non-invasively by echocardiogram in premature infants (12, 13). However, differences in neonatal myocardial compliance and heart rate make these measures challenging to reliably obtain and interpret. Further, these echocardiographic measures lack the ability to quantitate left atrial pressure. Small, single-center reports of catheterization hemodynamics in BPD-PH suggest that the median left atrial pressure is normal at 7–10 mmHg (14–17). No studies have explored the impact of LAH on outcomes or sought to explore risk factors for the development of LAH. We hypothesize that a subset of infants with BPD-PH have concomitant LAH at cardiac catheterization, which may impact clinical outcomes.

Methods

This retrospective cohort study evaluated patients with history of BPD-PH who underwent cardiac catheterization at Lucile Packard Children's Hospital Stanford from April 2010 to December 2021. Patients were included based on the following criteria: catheterization performed at our center, age <2 years at catheterization, PH as defined by criteria of mean PAP >20 mmHg, and diagnosis of bronchopulmonary dysplasia [based on gestational age and respiratory support at 36 weeks postmenstrual age (PMA)] (18). Infants with unrepaired simple shunt congenital heart disease [atrial septal defect (ASD), ventricular septal defect (VSD), and patent ductus arteriosus (PDA)] as well as pulmonary vein stenosis involving 2 or fewer veins were included. Patients with complex congenital heart disease, those who required cardiothoracic surgery, and those who had catheterization performed at an outside institution were excluded from this analysis. LAH was defined as a directly measured left atrial pressure (LAP) or pulmonary capillary wedge pressure (PCWP) ≥10 mmHg. In the presence of pulmonary vein stenosis, either direct LAP or PCWP from a lung segment with unobstructed pulmonary venous return was used. Acute vasoreactivity testing (AVT) was performed in a subset of patients. Hemodynamics were recorded at baseline and with maximal vasodilator therapy, which included 100% oxygen and/or 20 ppm inhaled nitric oxide, per interventional cardiologist discretion. Positive AVT testing was based on the Barst pediatric criteria of a decrease in mean PAP by at least 20% and an unchanged or increased cardiac index (19). Not all patients had arterial access during catheterization for accurate systemic vascular resistance to be calculated, so the Barst criteria of unchanged or decreased pulmonary to systemic vascular resistance ratio was unable to be utilized for AVT responsiveness in our cohort.

The primary aim of this study was to describe hemodynamics of an institutional cohort of patients with BPD-PH to determine incidence of LAH in this population. In this small pilot study, we explore the risk factors for LAH and examine the association of LAH with the composite outcome of tracheostomy and/or death. This study was approved by the Stanford University Institutional Review Board (IRB# 60898).

Statistical analysis

Variables were compared across LAH status using descriptive statistics. Results were presented in counts and percentages for categorical variables and median [interquartile range (IQR)] for continuous variables. Absolute standardized differences (d) were also reported, which measured the effect size for the comparison of the two groups. Standardized differences measure the absolute difference between two groups relative to their internal variation and are calculated for continuous and binary variables. For variables with more than two categories, standardized differences are calculated using Mahalanobis distance (20). Differences >0.2 may be considered small, 0.5 medium, and 0.8 large. A Cox regression model was used to determine if LAH is associated with the risk for the composite outcome of tracheostomy and/or death. Hazard ratio estimates and 95% confidence intervals were calculated. Univariate logistic regression models were conducted on an a priori set of clinically relevant variables to identify risk factors for LAH. Odds ratios and 95% confidence intervals were reported. Multivariable models were not considered because of the small number of patients with LAH. All analyses were performed using SAS 9.4 (Cary, NC).

Results

Between April 2010 and December 2021, 34 infants with BPD-PH underwent hemodynamic cardiac catheterization. Patient demographics and clinical characteristics are outlined in Table 1. There was a male predominance (65%) in this primarily non-Hispanic (74%) cohort. The median gestational age was 26.1 weeks PMA (IQR 24.9, 27.9 weeks PMA). Patients had median birth weight of 715 g (IQR 600, 895 g), with 35% (n = 12) meeting criteria for small for gestational age. A majority (n = 30, 88%) of the cohort had severe BPD. Congenital heart disease or pulmonary vein stenosis was present in 88% (n = 30) of the cohort, primarily with a PDA, ASD, or patent foramen ovale. Left ventricular systolic function was normal in all patients, and right ventricular systolic function was normal in 82% (n = 28) of patients, with the remainder having mild or moderate right ventricular systolic dysfunction. Patients were followed through April 1, 2022. Tracheostomy was performed in 32% (n = 11) of patients, and 18% (n = 6) of patients died (Table 1).

Clinical characteristics at time of catheterization and invasive hemodynamics are outlined in Table 2. Patients underwent catheterization at a median 3.4 months of age (IQR 3.1, 4.4 months), corresponding to a median 51.6 weeks PMA (IQR 42.3, 59.6 weeks PMA). Half of the cohort was supported at baseline with either invasive or non-invasive positive pressure ventilation (PPV) in the period preceding catheterization, which included infants requiring chronic intubation with mechanical ventilation, neonatal nasal intermittent positive pressure ventilation, and continuous or bilevel positive airway pressure. A majority (85%; n = 29) of infants were receiving scheduled diuretic therapy in the period preceding catheterization. Fifty-six percent of patients (n = 19) were on pulmonary vasodilator therapy at time of catheterization, most commonly with sildenafil in 47% (n = 16) of the total cohort. Baseline hemodynamics in our cohort demonstrated generally mild to moderate pulmonary vascular disease with a median mean PAP of 30 mmHg (IQR 27, 38 mmHg) and median indexed pulmonary vascular resistance (PVRi) 4.2 WU*m^2 (IQR 3.2, 7.3 WU*m^2). Median PCWP/LAP was 8 mmHg (IQR 8, 10 mmHg). Fifty percent (n = 17) of patients underwent intervention during catheterization: 14 patients underwent PDA device closure (2 of which were unsuccessful due to technical factors) and 3 underwent pulmonary vein balloon angioplasty. Hemodynamics utilized in analyses were obtained prior to intervention.

LAH was present in 32% (n = 11) of the cohort. Aside from PCWP/LAP, hemodynamics did not differ significantly between those with and without LAH. Patients with LAH were more likely to be small for gestational age (SGA), with 55% meeting SGA criteria and median birth weight at the 8th percentile (IQR 1, 56 percentile) compared to the non-LAH cohort, which had 26% SGA with median birth weight at the 39th percentile (IQR 9, 57 percentile, d = 0.61). Patients with LAH were more frequently supported at baseline with PPV in the period preceding catheterization (82%; n = 9) compared to the non-LAH cohort (35%; n = 8, d = 1.09). Patients with LAH were more likely to receive scheduled diuretic therapy prior to catheterization (100%; n = 11) compared to the non-LAH cohort (62%; n = 18, d = 0.75). Patients with LAH were also more likely to be on pulmonary vasodilator therapy, in particular sildenafil, prior to catheterization, with 64% (n = 7) of patients with LAH receiving sildenafil compared to 39% (n = 9) in the non-LAH cohort (d = 0.87). Both tracheostomy and death were more commonly encountered in the LAH cohort (d = 0.72 and 0.70, respectively).

Univariate logistic regression was performed on a priori selected clinically relevant variables to evaluate for risk of development of LAH, shown in Figure 1. Requirement of baseline invasive or non-invasive PPV preceding catheterization was associated with increased risk for LAH with an odds ratio (OR) of 8.44 (95% CI 1.46, 48.85). SGA status, pre-catheterization use of sildenafil, and presence of underlying congenital heart disease (including specifically the presence of a PDA) were not significantly associated with increased risk for LAH. The presence of LAH was associated with increased risk for the composite outcome of tracheostomy and/or death, with a hazard ratio (HR) of 6.32 (95% CI 1.72, 22.96, p = 0.005).

Acute vasodilator testing (AVT) was performed in 47% of patients (n = 16), including 55% (n = 6) of those with LAH and 43% (n = 10) of those without LAH. Hemodynamic response to

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TABLE 1 Patient demographics and clinical characteristics ($N = 34$).

	Total $N = 34$ n (%)	With left atrial hypertension (≥10 mmHg) $n = 11$ n (%)	Without left atrial hypertension (<10 mmHg) $n = 23$ n (%)	Absolute standardized difference (d)
Sex				0.31
Male	22 (65)	6 (55)	16 (70)	
Female	12 (35)	5 (45)	7 (30)	
Race				0.79
Asian	10 (29)	2 (18)	8 (35)	
Pacific Islander	2 (6)	0 (0)	2 (9)	
Black	1 (3)	0 (0)	1 (4)	
White	10 (29)	5 (45)	5 (22)	
Other	11 (32)	4 (36)	7 (30)	
Ethnicity				0.33
Hispanic	9 (26)	4 (36)	5 (22)	
Non-Hispanic	25 (74)	7 (64)	18 (78)	
Gestational age (weeks), median (IQR)	26.1 (24.9, 27.9)	25.6 (24.9, 28.0)	26.6 (24.9, 27.7)	0.03
Birthweight (g), median (IQR)	715 (600, 895)	700 (420, 960)	740 (630, 895)	0.29
Birthweight (percentile), median (IQR)	27 (7, 56)	8 (1, 56)	39 (9, 57)	0.41
SGA	12 (35)	6 (55)	6 (26)	0.61
Multiple congenital anomalies	7 (21)	3 (27)	4 (17)	0.61
BPD severity				0.48
Mild	2 (6)	1 (9)	1 (4)	
Moderate	2 (6)	0 (0)	2 (9)	
Severe	30 (88)	10 (91)	20 (87)	
Any type of CHD	30 (88)	9 (82)	21 (91)	0.28
PDA	21 (62)	7 (64)	14 (61)	0.06
ASD/PFO	21 (62)	7 (64)	14 (61)	0.06
VSD	4 (12)	1 (9)	3 (13)	0.13
PVS	4 (12)	2 (18)	2 (9)	0.28
Other	3 (9)	0 (0)	3 (13)	0.55
Echo LV systolic function				—
Normal	34 (100)	11 (100)	23 (100)	
Mildly depressed	—	—	—	
Moderately depressed	—	—	—	
Echo RV systolic function				0.55
Normal	28 (82)	10 (91)	18 (78)	
Mildly depressed	3 (9)	1 (9)	2 (9)	
Moderately depressed	3 (9)	0 (0)	3 (13)	
History of steroid use ($N = 33$)	18 (55)	7 (64)	11 (50)	0.28
Tracheostomy	11 (32)	6 (55)	5 (22)	0.72
Death	6 (18)	4 (36)	2 (9)	0.70

IQR, interquartile range; SGA, small for gestational age; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; PDA, patent ductus arteriosus; ASD, atrial septal defect; PFO, patent foramen ovale; VSD, ventricular septal defect; PVS, pulmonary vein stenosis; LV, left ventricular; RV, right ventricular.

AVT was variable, as depicted in Figure 2. Fewer patients with LAH responded positively to AVT (17%) compared to the non-LAH cohort (50%) ($d = 0.76$). While not all met criteria for positive AVT, some patients with LAH showed improvement in both mPAP and LAP with AVT. Conversely, a subset of those without LAH at baseline developed LAH with AVT (Figure 2).

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TABLE 2 Clinical characteristics at time of catheterization and invasive hemodynamics ($N = 34$).

	Total $N = 34$ n (%)	With left atrial hypertension (≥10 mmHg) $n = 11$ n (%)	Without left atrial hypertension (<10 mmHg) $n = 23$ n (%)	Absolute standardized difference (d)
Age at catheterization (months), median (IQR)	3.4 (3.1, 4.4)	3.4 (3.2, 4.5)	3.4 (2.9, 4.4)	0.14
Corrected gestational age at catheterization (weeks PMA), median (IQR)	51.6 (42.3, 59.6)	53.4 (42.7, 58.3)	48.0 (42.1, 60.1)	0.16
PPV preceding catheterization	17 (50)	9 (82)	8 (35)	1.09
Scheduled diuretic preceding catheterization	29 (85)	11 (100)	18 (62)	0.75
Pulmonary hypertension medications preceding catheterization	19 (56)	8 (73)	11 (47)	0.53
Inhaled Nitric Oxide	3 (9)	1 (9)	2 (9)	0.51
Sildenafil	16 (47)	7 (64)	9 (39)	0.87
Bosentan	3 (9)	3 (27)	0 (0)	0.67
Treprostinil	2 (6)	2 (18)	0 (0)	0
Tadalafil	1 (3)	1 (9)	0 (0)	0.45
Baseline catheterization data				
Respiratory support–RA	31 (91)	10 (91)	21 (91)	0.01
Respiratory support–Oxygen >50%	2 (6)	1 (9)	1 (4)	0.19
Respiratory support–iNO	2 (6)	1 (9)	1 (4)	0.19
Systolic PAP (mmHg), median (IQR)	45 (38, 53)	42 (35, 57)	45 (40, 52)	0.01
Diastolic PAP (mmHg), median (IQR)	22 (17, 26)	23 (18, 29)	22 (15, 26)	0.45
Mean PAP (mmHg), median (IQR)	30 (27, 38)	32 (27, 44)	30 (24, 38)	0.27
LAP/PCWP (mmHg), median (IQR)	8 (8, 10)	11 (10, 12)	8 (7, 8)	3.43
Qp:Qs, median (IQR)	1.4 (1.0, 1.9)	1.3 (1.0, 2.0)	1.4 (1.0, 1.9)	0.27
CI (L/min/m^2), median (IQR)	3.4 (3.1, 4.4)	3.4 (3.2, 4.5)	3.4 (2.9, 4.4)	0.05
PVRi (WU*m^2), median (IQR)	4.2 (3.2, 7.3)	3.5 (2.9, 8.2)	4.3 (3.5, 7.3)	0.08
Acute vasodilator testing performed	16 (47)	6 (55)	10 (43)	0.22
Vaso-reactive ($N = 16$)	6 (38)	1 (17)	5 (50)	0.76
Intervention at catheterization	17 (50)	7 (64)	10 (43)	0.48
PDA device closure	14 (82)	5 (71)	9 (90)	
Pulmonary vein balloon angioplasty	3 (18)	2 (29)	1 (10)	

IQR, interquartile range; PMA, postmenstrual age; PPV, positive pressure ventilation; RA, room air; iNO, inhaled nitric oxide; PAP, pulmonary arterial pressure; LAP, left atrial pressure; PCWP, pulmonary capillary wedge pressure; Qp:Qs, pulmonary to systemic flow ratio; CI, cardiac index; PVRi, indexed pulmonary vascular resistance; PDA, patent ductus arteriosus.

Discussion

This retrospective cohort study is the first to describe the incidence of LAH in patients with BPD-PH. We found LAH in nearly one-third of infants whose hemodynamics have been evaluated by cardiac catheterization. The need for baseline PPV preceding catheterization was associated with increased risk for LAH. LAH was associated with increased risk of tracheostomy and/or death.

The pulmonary vascular changes associated with BPD that lead to PH are well-described (7–9). However, LAH as a potential contributor to the cardiopulmonary status of a premature infant is poorly understood. Premature birth alters myocardial structure, with cardiomyocyte hypertrophy and increased collagen deposition (21). This may predispose to altered diastolic function, with potential for resultant LAH. Cardiac shunt lesions, particularly a persistent PDA, are common in premature infants (22). With a hemodynamically significant PDA, left heart volume overload can also cause clinically relevant LAH, particularly in preterm infants who may be predisposed to diastolic dysfunction. Impaired diastolic function has been demonstrated by echocardiographic studies, with hemodynamically significant PDA being a potential contributor to these indices (12, 13, 23). However, these remain indirect markers of diastolic dysfunction, and there is some evidence that brings into question the reliability of these markers in patients with pulmonary hypertension (24).

Therefore, we examined directly measured PCWP/LAP in the catheterization lab. One limiting factor is the lack of definition for hemodynamic norms, particularly normal

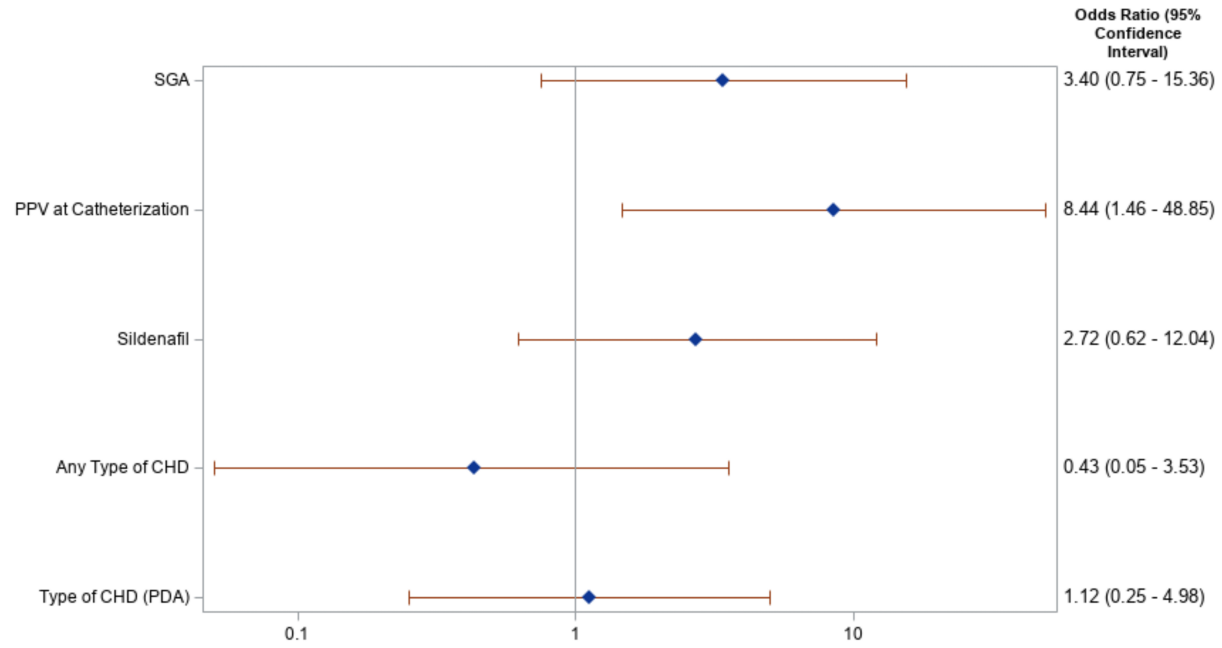

FIGURE 1
Forest plot of risk factors for left atrial hypertension: Risk for left atrial hypertension for select clinical factors is demonstrated in this Forest plot, along with associated odds ratio and p-value. Positive pressure ventilation (PPV) was the only variable that demonstrated significant risk for left atrial hypertension. SGA, small for gestational age; PPV, positive pressure ventilation; CHD, congenital heart disease; PDA, patent ductus arteriosus.

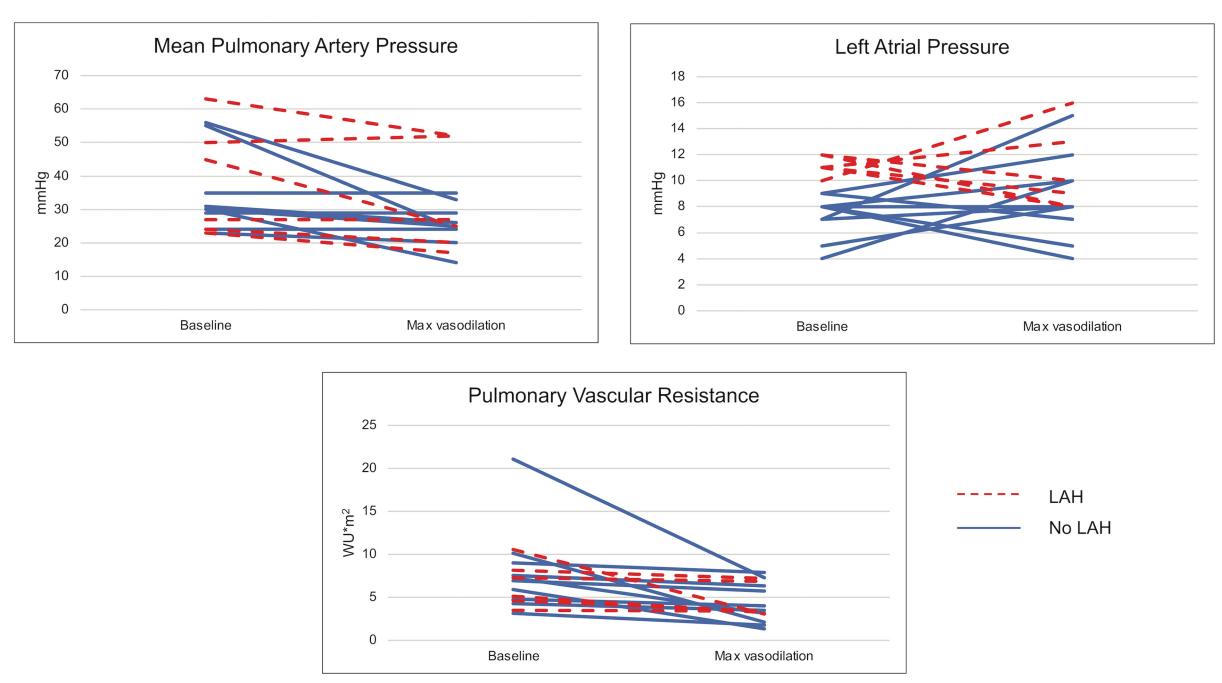

FIGURE 2
Hemodynamic changes with acute vasodilator testing. Changes in mean pulmonary artery pressure, left atrial pressure, and pulmonary vascular resistance are demonstrated at baseline and with maximal vasodilation (100% FiO2 ± inhaled nitric oxide) utilized in acute vasodilator testing, which was performed in 16 patients.

left atrial pressure, in premature infants. The formal cut-off for post-capillary pressure elevation is a PCWP of ≥ 15 mmHg according to the World Symposium on Pulmonary Hypertension classification schema (25). However, normal LV diastolic pressures in healthy children have been demonstrated to be significantly lower than this at a mean of 7.5 mmHg (standard deviation 2.2 mmHg) (26). Premature infants with BPD may develop clinically relevant symptoms at a lower LA pressure than 15 mmHg, with an initial case series highlighting clinically significant pulmonary edema related to diastolic dysfunction in premature infants with PCW pressures of 12 and 17 mmHg (11). For these reasons, our group used a cut-off of 10 mmHg to define LAH to be inclusive of patients with mild, but potentially clinically important, elevations of LA pressure.

The increased use of diuretics and positive pressure ventilation in patients with LAH suggests that even mild LAH may correlate with increased clinical symptoms, although causality cannot be attributed. Further, a majority of this cohort had underlying CHD with left to right shunt, which likely contributed to the benefit of diuretic therapy. Additionally, LAH was associated with increased risk for the composite outcome of death and/or tracheostomy. It is unclear whether worse lung function predisposes to LAH or if LAH worsens parenchymal lung disease by causing pulmonary edema that increases need for diuretics and ventilator support. Larger studies will be required to investigate this further.

Congenital heart disease was not associated with LAH in our cohort. We anticipated that the presence of a hemodynamically significant PDA would be a significant contributor to LAH. Contrary to our initial hypothesis, CHD, including PDA, was not associated with significantly increased risk for LAH by univariate analysis. This is particularly notable given that many of the PDAs present in our cohort were likely hemodynamically significant, with 41% undergoing attempted PDA device closure at time of catheterization. Additionally, pulmonary vasodilator use was not associated with worse LAH. These medications were frequently in use before catheterization, particularly as expert consensus suggests the initiation of pulmonary vasodilator monotherapy without catheterization is reasonable in uncomplicated BPD-PH when balancing risks associated with catheterization (27, 28). While the increased pulmonary blood flow that may result from pulmonary vasodilator therapy may pose theoretic risk for LAH in the less compliant myocardium of the premature infant, the use of sildenafil was not associated with increased risk for LAH in our cohort. Similarly, few patients showed significant worsening of LAH with AVT, although testing did unmask LAH in a few subjects.

Limitations of this study include its retrospective nature and small sample size in a single center. The small size and heterogeneous nature of the population precluded multivariate analysis. Selection bias may be present as we included only patients who underwent cardiac catheterization. At our center, infants with BPD-PH are often treated with diuretic therapy and pulmonary vasodilator monotherapy before consideration of cardiac catheterization, making our study potentially skew toward a sicker cohort in whom catheterization was required to guide clinical management. However, the relatively mild elevation of pulmonary artery pressure and pulmonary vascular resistance might suggest this is not the case. In this cohort of infants with BPD-PH, cardiac catheterization was performed under general anesthesia with patients intubated and mechanically ventilated with optimized respiratory mechanics. As such, the hemodynamics may reflect the "best case scenario" rather than the clinical baseline. Conversely, mechanical positive pressure ventilation in the catheterization lab may negatively impact bi-ventricular compliance and result in increased left atrial pressure compared to clinical baseline in those who who are not supported with chronic PPV (29). Interpretation of the hemodynamics (and response to AVT) may also be confounded by the fact that most patients were treated with pulmonary vasodilator therapy and diuretics at time of catheterization.

This small pilot study is the first to examine the incidence and clinical impact of LAH in patients with BPD-PH. Clinically, this study raises the question of whether some patients should undergo earlier hemodynamic evaluation with cardiac catheterization to assess for LAH. Based on this pilot data, one may consider low threshold for diuretic therapy in premature infants with PH. Earlier catheterization should be considered in patients with echocardiographic evidence of PH who have increasing diuretic requirements or inability to wean respiratory support, especially following initiation of pulmonary vasodilator therapy. Additional larger, multi-institutional studies are needed to further define the definition of LAH in this population and further investigate its clinical impact on BPD-PH.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Stanford University Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

RS contributed to project design, data collection/analysis, and was responsible for primary manuscript composition. MDT and DB performed statistical planning and analysis. RH contributed as senior author with primary role in project design, data analysis, and manuscript preparation. SB, GA,

MT, and AM contributed specialty-specific input in project development and manuscript review in the fields of neonatology, interventional pediatric cardiology, pediatric pulmonology, and neonatology, respectively. All authors demonstrated significant academic contribution to justify authorship and were involved in manuscript review and final manuscript approval.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Michael Portman,
University of Washington, United States

REVIEWED BY
Nicolas Madsen,
University of Texas Southwestern Medical Center, United States
Brian Soriano,
Seattle Children's Hospital, United States

*CORRESPONDENCE
Catherine M. Avitabile
avitabilec@chop.edu

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Skeletal muscle deficits are associated with worse exercise performance in pediatric pulmonary hypertension

Catherine M. Avitabile[1,2]*, Michael G. McBride[1], Matthew A. Harris[1,2], Kevin K. Whitehead[1,2], Mark A. Fogel[1,2], Stephen M. Paridon[1,2] and Babette S. Zemel[2,3]

[1]Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [2]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States, [3]Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, United States

Background: Skeletal muscle deficits are associated with worse exercise performance in adults with pulmonary hypertension (PH) but the impact is poorly understood in pediatric PH.

Objective: To study muscle deficits, physical inactivity, and performance on cardiopulmonary exercise test (CPET) and exercise cardiac magnetic resonance (eCMR) in pediatric PH.

Methods: Youth 8–18 years participated in a prospective, cross-sectional study including densitometry (DXA) for measurement of leg lean mass Z-score (LLMZ), handheld dynamometer with generation of dominant and non-dominant handgrip Z-scores, Physical Activity Questionnaire (PAQ), CPET, and optional eCMR. CPET parameters were expressed relative to published reference values. CMR protocol included ventricular volumes and indexed systemic flow at rest and just after supine ergometer exercise. Relationships between LLMZ, PAQ score, and exercise performance were assessed by Pearson correlation and multiple linear regression.

Results: There were 25 participants (13.7 ± 2.8 years, 56% female, 64% PH Group 1, 60% functional class I); 12 (48%) performed both CPET and eCMR. Mean LLMZ (−0.96 ± 1.14) was associated with PAQ score ($r = 50$, $p = 0.01$) and with peak oxygen consumption (VO_2) ($r = 0.74$, $p = < 0.001$), VO_2 at anaerobic threshold ($r = 0.65$, $p < 0.001$), and peak work rate ($r = 0.64$, $p < 0.01$). Higher handgrip Z-scores were associated with better CPET and eCMR performance. On regression analysis, LLMZ and PAQ score were positively associated with

peak VO_2, while handgrip Z-score and PAQ score were positively associated with peak work rate.

Conclusion: Muscle mass and strength are positively associated with exercise performance in pediatric PH. Future studies should determine the effect of rehabilitation programs on muscle properties and exercise performance.

KEYWORDS

pediatric pulmonary hypertension, skeletal muscle, exercise, densitometry, cardiac magnetic resonance imaging

Introduction

Pediatric pulmonary hypertension (PH) is associated with various vascular, cardiac, pulmonary, and systemic conditions. Without treatment, the disease leads to right ventricular dysfunction, right ventricular failure, and death. While therapies have improved in recent years (1, 2), long-term outcomes remain poor. Patients report low quality of life in the face of significant morbidity and mortality risk (3, 4). Exercise intolerance is common in PH patients, significantly impacting quality of life and prognosis. While cardiopulmonary status affects exercise performance, the contribution of peripheral factors, including skeletal muscle dysfunction, is increasingly recognized (5). Skeletal muscle dysfunction is associated with worse 6-min walk distance (6 MWD) in adults with idiopathic pulmonary arterial hypertension (IPAH) (6). Similarly, we previously reported marked deficits in densitometry (DXA)-measured leg lean mass, a surrogate marker of skeletal muscle, in youth with PH in association with inactivity and worse 6 MWD (7). In other studies, skeletal muscle atrophy, impaired peripheral oxygen extraction, and reduced muscle contractility suggest that PH patients exhibit a generalized "myopathy" similar to patients with left heart failure (8–11). The skeletal muscle pump is critically important to augmentation of systemic venous return and pulmonary blood flow with erect exercise (12). Skeletal muscle dysfunction may critically hinder this mechanism in PH patients. Therefore, we sought to expand on our prior findings by characterizing leg lean mass Z-score (LLMZ) and muscle strength in a different cohort of pediatric PH patients and to explore the associations between muscle deficits, self-reported physical activity, and measures of exercise performance on cardiopulmonary exercise test (CPET) and exercise cardiac magnetic resonance (eCMR).

Abbreviations: 6 MWD, 6-min walk distance; BMDCS, Bone Mineral Density in Childhood Study; CPET, cardiopulmonary exercise test; DXA, densitometry; eCMR, exercise cardiac magnetic resonance; IPAH, idiopathic pulmonary arterial hypertension; LLMZ, leg lean mass Z-score; NHANES, National Health and Nutrition Examination Survey; PAQ, physical activity questionnaire; PH, pulmonary hypertension; VAT, ventilatory anaerobic threshold; VE/VCO_2, ventilatory equivalents of carbon dioxide; VO_2, oxygen consumption.

Materials and methods

Study population

Youth ages 8–18 years with World Symposium of PH (WSPH) diagnostic Groups 1–4 and functional class I or II were prospectively enrolled in a cross-sectional study from 2018 to 2021. Exclusion criteria included pregnancy, functional class III or IV, single ventricle physiology, moderate to severe chronic kidney disease (stage 3 or greater), severe hepatic impairment (transaminases $>$ 2 times the upper limit of normal), pacemaker, defibrillator, or other metal that would interfer with imaging, and significant developmental delay or inability to comply with verbal English instructions in order to complete the study procedures. Fully informed, written consent was obtained from the parent/legal guardian of participants $<$ 18 years and of participants 18 years of age. In addition, age-appropriate informed assent was obtained from participants $<$ 18 years. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board.

Study procedures

Pulmonary hypertension history and standard of care testing

The medical record was queried for WSPH diagnostic group, World Health Organization (WHO) functional class, medications, and standard of care testing including last echocardiogram, 6-min walk test (within 3 months), cardiac catheterization data, and brain-type natriuretic peptide. Six-minute walk tests were performed according to American Thoracic Society guidelines (13).

Anthropometry and tanner stage

Weight was measured to the nearest 0.1 kg with a digital electronic stand-on scale. Height and sitting height were measured to the nearest 0.1 cm with a wall-mounted stadiometer in order to calculate leg length (leg length = height - sitting height). Tanner stage was determined via a validated self-assessment tool (14).

Heath-related quality of life

Participants and parents/guardians completed the Pediatric Cardiac Quality of Life Inventory, a reliable and validated instrument of disease specific quality of life for patients 8–18 years of age with congenital or acquired heart disease (15). Disease impact and psychosocial impact subscores were summed to generate a total score with higher scores (maximum 100 points) representing better health-related quality of life.

Physical activity questionnaire

Participants completed the Physical Activity Questionnaire (PAQ) for Older Children or Adolescents (PAQ-C and PAQ-A), 7-day recall instruments designed to assess moderate to vigorous physical activity (16–18). The 5-point scoring scale was used to calculate a final summary score from the means of scores for each question. Average scores $>$ 3 are reported in healthy populations (16).

Vitamin D levels

Quantification of circulating 25 (OH) vitamin D was performed by HPLC tandem mass-spectrometry (19). Vitamin D deficiency was defined as serum level less than 20 ng/mL (20).

Body composition

Whole body lean and fat mass were measured with a Hologic Delphi densitometer (Bedford, Massachusetts, USA) in array mode (software V.12.4). Measurements were performed with standard supine positioning techniques with participants wearing scrubs to minimize scan variability. Urine pregnancy test was performed prior to DXA in female participants. Whole body lean mass was calculated as fat-free mass minus bone mineral content. Leg lean mass was used as a measure of skeletal muscle, given the previously reported concerns with the use of whole body lean mass as a representation of muscle mass (21). Calibration was performed daily with a hydroxyapatite phantom and weekly with a whole-body phantom. Coefficients of variation ranged from 1 to 4% (22).

Muscle strength testing

Bilateral forearm strength was measured with a handgrip dynamometer (Takei, Tokyo, Japan) (23). Hand dominance was determined by which hand the participant used to hold a pencil. The participant stood upright with the shoulder adducted holding the dynamometer, not touching the trunk. The handle was adjusted to the hand size of the participant, and no extra body movement was allowed during testing. For each hand, 3 maximal effort trials lasting 4–5 s interspersed with 60-s rests were carried out. The highest value was retained for analysis. Lower extremity strength (knee and ankle) was assessed using the Biodex Multi-Joint System 3 Pro (Biodex Medical Systems, Inc., Shirley, NY, USA) (24). For the knee, peak quadricep muscle torque (ft-lbs) was measured in knee flexion and extension. Participants sat with their thighs at an angle of 110° to the trunk. The trunk and both thighs were stabilized with belts. The tested knee was positioned at 90° flexion, and the mechanical axis of the dynamometer was aligned with the lateral epicondyle of the knee. Each participant performed 10 concentric contractions at 120°/s (flexion and extension) of both sides, and the highest value was recorded. For the ankle, peak calf muscle torque (ft-lbs) in dorsiflexion and plantarflexion were measured in triplicate with the foot placed in 20 degrees of plantar flexion, and the highest value was recorded (24, 25). Peak muscle torque was adjusted for patient age.

Cardiopulmonary exercise test

Patients exercised to their maximum ability on an electronically braked cycle ergometer (Ergometrics 800, SensorMedics, Yorba Linda, CA). A 12-lead electrocardiogram was obtained at rest in supine, sitting, and standing positions. Three minutes of pedaling in an unloaded state were followed by a ramp increase in work rate to achieve predicted peak work rate in 10–12 min of cycling time (26). Cardiac rhythm and pulse oximetry were monitored throughout the study. Blood pressure was measured at rest and every 3 min during exercise and recovery by auscultation. Metabolic data were obtained throughout the study and for the first 2 min of recovery on a breath-by-breath basis using a metabolic cart (SensorMedics V29, Yorba Linda, CA or similar). Ventilatory anaerobic threshold (VAT) was measured by the V-slope method (27). Peak oxygen consumption (VO_2) and VO_2 at VAT were normalized to the percentage expected for age, gender, and body size (28). O_2 pulse was calculated by dividing peak VO_2 by maximum heart rate. And expressed in milliliters per beat. A maximal test was defined as a respiratory exchange ratio $\geq$ 1.10 (29).

Exercise cardiac magnetic resonance

Participants $\geq$ 11 years of age could consent to a non-sedate, resting and exercise CMR protocol (30). The resting protocol consisted of a contiguous axial stack of static steady-state free precession images used for multiplanar anatomic reconstruction, both segmented and free-breathing real time cine short axis stacks, and through-plane retrospectively gated, respiratory-averaged phase-contrast MR across the superior and inferior vena cavae, branch pulmonary arteries, aortic valve, and descending aorta at the level of the diaphragm. After resting CMR image acquisition, the participant was slid partially out from the MR bore to perform lower limb exercise using an

MR-compatible supine bicycle ergometer (Lode BV, Groningen, Netherlands). Heart rate was monitored continuously. An initial workload of 20 Watts was increased 20 Watts/minute to achieve the heart rate associated with VAT on the prior CPET. Exercise was suspended, the participant's feet were removed from the ergometer pedals, and the participant was returned to isocenter for imaging (generally within 5–10 s). A free-breathing real time cine short axis stack was performed; this method has been previously validated against breath-held segmented short axis imaging (31, 32). As breath-holding is not uniform after exercise, respiratory-averaged segmented phase-contrast MR measurements of the aorta, superior vena cava, and descending aorta were performed. Descending aorta flow is substituted for inferior vena cava flow due to difficulty in maintaining inferior vena cava position at exercise (33). Flows and volumes were segmented using cvi42 software 5.13.7 (Circle Cardiovascular Imaging Inc.). Cardiac index was calculated as the product of stroke volume and heart rate, indexed to body surface area. Indexed systemic blood flow was calculated as the sum of superior vena cava and descending aorta flow, indexed to body surface area.

Statistical analysis

Growth and body composition variables were converted to Z-scores (standard deviation scores) as previously described (7, 21, 34). The 2,000 Centers for Disease Control and Prevention growth charts were used to calculate sex-specific Z-scores for height, weight, and body mass index relative to age (35). Data from > 2,000 healthy, typically developing children from multiple ethnic groups, ages 5–19 years, enrolled in the Bone Mineral Density in Childhood Study (BMDCS) (36, 37), a multicenter longitudinal DXA study, were used to compare participants' growth Z-scores to a contemporary cohort. These reference data were also used to calculate sex- and race-specific LLMZ relative to age using the LMS method (38). Body composition measures are highly correlated with height and PH physiology is associated with impaired linear growth (39). Therefore, LLMZ was further adjusted for leg length Z-score (40).

Sex-specific reference curves for dominant and non-dominant handgrip were generated using data from the 2011–2012 and 2013–2014 releases of the US National Health and Nutrition Examination Survey (NHANES) using the LMS method (38) and implemented in R programming language using the Generalized Additive Models for Location, Scale, and Shape (GAMLSS library) in R (41).

Standard descriptive statistics [mean ± standard deviation or median (interquartile range)] were used to summarize baseline PH characteristics, LLMZ, muscle strength, quality of life scores, and CPET and eCMR data. Differences in body composition Z-scores between PH participants and the BMDCS reference data were assessed using one-sample Student's *t*-test. Analyses within the PH group included correlations between LLMZ and continuous variables (e.g., indexed pulmonary vascular resistance) assessed by Pearson or Spearman correlation and comparisons of LLMZ according to categorical variables (e.g., diagnostic group or functional class). Associations between muscle mass and strength, physical activity, and exercise parameters were assessed by Pearson correlation and multiple linear regression. All analyses were conducted using Stata 16.1 with two-sided tests of hypotheses and a p-value < 0.05 as the criterion for clinical significance.

Results

Demographic and clinical characteristics of the 25 participants are displayed in **Table 1**. The cohort was 56% female and majority white. Mean height Z-score was –0.24 ± 1.24 while mean BMI Z-score was 0.19 ± 0.93. Most patients (64%) were classified as WSPH Group 1 (pulmonary arterial hypertension), but 24% of patients were classified as WSPH group 3 (PH due to lung disease). Of the 16 participants in WSPH Group 1, there were 10 with idiopathic or heritable PAH and 6 with PAH after repair of congenital heart disease. No participants with congenital heart disease had unrepaired cyanotic lesions or significant residual shunts. More patients were WHO functional class I but patients in functional class II enrolled as well. The most common medications were tadalafil and ambrisentan. Twenty-eight percent of the cohort met criteria for vitamin D deficiency. Mean brain natriuretic peptide and hemoglobin levels were within normal limits for our laboratory. Mean tricuspid annular plane systolic excursion Z-score was –2.5 ± 3.2 reflecting decreased right ventricular function. Participants achieved an average 6 MWD of 636 ± 113 meters reflecting good functional status. Cardiac catheterization data were available in 23 participants (90%) at median 1.42 years prior to the study visit. Mean pulmonary artery pressure was 33.1 ± 12.0 mm Hg and indexed pulmonary vascular resistance was 6.2 ± 3.0 indexed Wood units. PAQ scores were lower than reported for healthy populations. Average quality of life score was less than 70 for both participants and parents/guardians.

Skeletal muscle mass and strength data are shown in **Table 2**. Mean LLMZ was markedly decreased at –0.96 ± 1.14, equivalent to the 17th percentile. Dominant (D-HGZ) and non-dominant (ND-HGZ) were also very low with mean D-HGZ of –1.33 ± 1.37 equivalent to the 9th percentile.

Table 3 includes CPET and eCMR data. Baseline oxygen saturation was 97.7 ± 1.5% with decrease to 91.5 ± 8.3% (range 71–100) with CPET. On CPET, participants performed lower than predicted compared to healthy reference data. Percent predicted peak VO_2 was approximately 71% while percent predicted VO_2 at VAT was approximately 80%. Participants only achieved a peak work rate 59% predicted for demographics and

TABLE 1 Demographic and clinical characteristics of participants (*N* = 25).

Variable	N (%) or mean ± SD/median (IQR)
Age, *y*	13.7 ± 2.8
Female	14 (56)
Race	
White	16 (64)
Black/African American	7 (28)
Unknown/not reported	2 (8)
Hispanic or Latino	2 (8)
Height Z-score	−0.24 ± 1.24
Weight Z-score	0.01 ± 1.20
BMI Z-score	0.19 ± 0.93
WSPH classification	
Group 1—PAH	16 (64)
Group 2—PH due to left heart disease	2 (8)
Group 3—PH due to lung disease	6 (24)
Group 4—Chronic thromboembolic PH	1 (4)
WHO functional class	
I	15 (60)
II	10 (40)
Medications	
Sildenafil	2 (8)
Tadalafil	16 (64)
Ambrisentan	15 (60)
Macitentan	1 (4)
Treprostinil SQ	4 (16)
Treprostinil oral	6 (24)
Vitamin OH-D level, *ng/mL*	26.8 ± 13.3
Vitamin D deficiency	7 (28)
BNP, *pg/mL*	22.5 (10.3, 40.1) (Range 10–150.5)
Hemoglobin, *g/dL*	12.9 ± 1.0
TAPSE by echocardiogram, *cm*	1.8 ± 0.5
TAPSE Z-score	−2.5 ± 3.2
6 MWD, *m*	636 ± 113
Cardiac catheterization data	
Interval from study visit, *y*	1.42 (0.54, 1.92)
Mean PA pressure, *mm Hg*	33.1 ± 12.0
PA/Ao ratio	0.5 ± 0.2
Cardiac index, $L/min/m^2$	3.7 ± 0.8
PVRi, *iWU*	6.2 ± 3.0
PVRi/SVRi ratio	0.3 ± 0.2
Self-reported scores	
PAQ score	1.9 ± 0.6
PCQLI participant score	67.6 ± 17.7
PCQLI parent/guardian score	68.3 ± 16.3

SD, standard deviation; IQR, interquartile range; y, year; BMI, body mass index; WSPH, World Symposium of Pulmonary Hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; WHO, World Health Organization; SQ, subcutaneous; BNP, brain natriuretic peptide; TAPSE, tricuspid plane systolic excursion; 6 MWD, 6-min walk distance; PA, pulmonary artery; Ao, aorta; PVRi, indexed pulmonary vascular resistance; SVRi, indexed systemic vascular resistance; PAQ, physical activity questionnaire; PCQLI, pediatric cardiac quality of life inventory.

TABLE 2 Skeletal muscle assessment.

Variable	Mean ± SD
LLMZ	−0.96 ± 1.14
Hand grip	
D-HGZ	−1.33 ± 1.37
ND-HGZ	−1.14 ± 1.50
Lower extremity biodex, *ft-lbs*	
Knee flexion	25.5 ± 12.3
Knee extension	53.8 ± 23.4
Ankle flexion	15.2 ± 5.4
Ankle extension	29.0 ± 12.1

LLMZ, leg lean mass Z-score; D-HGZ, dominant handgrip Z-score; ND-HGZ, non-dominant handgrip Z-score.

TABLE 3 Exercise performance data.

CPET			Mean ± SD
Peak VO_2, *mL/kg/min*			29.3 ± 6.6
Percent predicted peak VO_2			0.71 ± 0.21
O_2 pulse, *mL/beat*			8.3 ± 2.3
VO_2 at VAT, *mL/kg/min*			19.3 ± 4.3
Percent predicted VO_2 at VAT			0.80 ± 0.20
Work, *watts*			92.8 ± 28.3
Percent predicted work			0.59 ± 0.21
Work at VAT, *watts*			44.0 ± 17.2
VE/VCO_2 ratio			32.6 ± 4.8
CMR	**Rest**	**Exercise**	***p*-value for change from rest to exercise**
RV EDVi, mL/m^2	97.9 ± 17.2	88.5 ± 17.8	0.21
RV ESVi, mL/m^2	41.5 ± 9.6	33.4 ± 10.6	0.07
RV SVi, mL/m^2	56.6 ± 13.1	55.0 ± 11.9	0.76
RV EF, %	60.1 ± 10.1	62.6 ± 8.4	0.52
RV cardiac index, $L/min/m^2$	4.4 ± 1.0	5.7 ± 1.4	0.02
LV EDVi, mL/m^2	81.7 ± 18.9	77.1 ± 20.1	0.57
LV ESVi, mL/m^2	27.8 ± 7.2	20.5 ± 10.0	0.06
LV SVi, mL/m^2	54.0 ± 12.9	56.6 ± 13.1	0.62
LV EF, %	66.1 ± 4.2	73.9 ± 7.6	<0.01
LV cardiac index, $L/min/m^2$	4.2 ± 0.8	5.9 ± 1.6	<0.01
Systemic flow, $mL/min/m^2$	4.0 ± 0.8	6.6 ± 1.9	<0.001

CPET, cardiopulmonary exercise test; VO_2, oxygen consumption; VAT, ventilatory anaerobic threshold; CMR, cardiac magnetic resonance; RV, right ventricular; EDVi, end-diastolic volume indexed; ESVi, end-systolic volume indexed; SVi, stroke volume indexed; EF, ejection fraction; LV, left ventricular.

body size. Reference data are not available for work rate at VAT. Resting and exercise CMR data are displayed. Right and left ventricular cardiac index and systemic blood flow increased with exercise.

LLMZ was associated with disease-specific factors. LLMZ was positively associated with hemoglobin (r = 0.44, p = 0.03)

and negatively associated with brain type natriuretic peptide ($r = -0.40$, $p = 0.05$), mean pulmonary artery pressure ($r = -0.54$, $p < 0.01$), and indexed pulmonary vascular resistance ($r = -0.50$, $p = 0.02$) but was not associated with tricuspid annular plane systolic Z-score. LLMZ was higher in those with higher PAQ scores ($r = 0.50$, $p = 0.01$).

LLMZ, muscle strength, and PAQ score were associated with performance on CPET and eCMR (Table 4). LLMZ, both D-HGZ and ND-HGZ, and PAQ score were associated with percent predicted peak VO_2, percent predicted VO_2 at VAT, and percent predicted work (Figures 1–3). LLMZ was associated with O_2 pulse on CPET ($r = 0.41$, $p = 0.04$) while D-HGZ was not. D-HGZ was associated with most recent 6 MWD ($r = 0.44$, $p = 0.03$). D-HGZ, ND-HGZ, and PAQ score were also associated with change in systemic flow from rest to exercise on eCMR, while LLMZ was not ($r = 0.51$, $p = 0.1$).

The associations between lower extremity strength by Biodex and exercise performance were variable. Ankle extension was associated with change in systemic flow from rest to exercise ($r = 0.69$, $p = 0.04$). Both knee extension and flexion were associated with peak work (not percent predicted) ($r = 0.52$, $p = 0.02$ for extension; $r = 0.48$, $p = 0.03$ for flexion), possibly because Z-scores are not available for the Biodex variables.

Results from multiple linear regression models testing the effect of skeletal muscle and physical activity variables on exercise performance are shown in Table 5. LLMZ and PAQ score were positively associated with peak VO_2, while handgrip Z-score and PAQ score were positively associated with peak work rate. No factors were associated with the change in systemic flow from rest to exercise on eCMR.

There were no differences in LLMZ, PAQ, CPET, or eCMR findings in participants with Group 2 PH vs. other classifications. The study findings were unchanged when participants with Group 2 PH were excluded. There were some differences in LLMZ and exercise performance based on medication regimen. Participants on subcutaneous treprostinil had lower LLMZ (-2.02 ± 1.03 vs. -0.76 ± 1.06, $p = 0.04$), percent predicted VO_2 (0.49 ± 0.11 vs. 0.75 ± 0.21, $p = 0.02$), percent predicted VO_2 at VAT (0.54 ± 0.13 vs. 0.86 ± 0.17, $p < 0.01$), and percent predicted work (0.41 ± 0.10 vs. 0.63 ± 0.20, $p = 0.05$) compared to those not on subcutaneous treprostinil. Interestingly, participants on oral treprostinil demonstrated greater change in systemic flow with exercise [4.56 ± 1.56 ($n = 3$ with cCMR) vs. 2.02 ± 0.85 ($n = 7$ with eCMR), $p < 0.01$] and higher PAQ (2.3 ± 0.6 vs. 1.8 ± 0.6, $p = 0.06$), D-HGZ (-0.30 ± 1.62 vs. -1.67 ± 1.14, $p = 0.03$), and ND-HGZ (-0.02 ± 1.74 vs. -1.45 ± 1.28, $p = 0.04$) compared to those participants not on oral treprostinil. Participants on ambrisentan demonstrated lower percent predicted VO2 at VAT (0.73 ± 0.22 vs. 0.91 ± 0.13, $p = 0.04$) compared to those not on ambrisentan.

No adverse events occurred with exercise testing.

TABLE 4 Associations between skeletal muscle, physical activity, and exercise performance.

Variable	CPET or eCMR parameter	r	*P*-value
LLMZ	Percent predicted VO_2	0.74	<0.001
	Percent predicted VO_2 at VAT	0.65	<0.001
	Percent predicted work	0.64	<0.01
	O_2 pulse	0.41	0.04
D-HGZ	Percent predicted VO_2	0.61	<0.01
	Percent predicted VO_2 at VAT	0.46	0.03
	Percent predicted work	0.73	<0.001
	Change in systemic flow from rest to exercise	0.74	0.02
ND-HGZ	Percent predicted VO_2	0.63	<0.001
	Percent predicted VO_2 at VAT	0.52	0.01
	Percent predicted work	0.74	<0.001
	Change in systemic flow from rest to exercise	0.70	0.02
PAQ	Percent predicted VO_2	0.62	0.001
	Percent predicted VO_2 at VAT	0.48	0.02
	Percent predicted work	0.53	<0.01
	Change in systemic flow from rest to exercise	0.70	0.02

CPET, cardiopulmonary exercise test; eCMR, exercise cardiac magnetic resonance; LLMZ, leg lean mass Z-score; VO_2, oxygen consumption; VAT, ventilatory anaerobic threshold; D-HGZ, dominant handgrip Z-score; ND-HGZ, non-dominant handgrip Z-score; PAQ, physical activity questionnaire.

Discussion

In this study, we demonstrated marked deficits in skeletal muscle mass and strength in association with worse exercise performance on CPET and eCMR in youth with PH. Lower skeletal muscle mass was associated with physical inactivity. In regression models, skeletal mass, strength, and physical activity were positively associated with exercise performance on CPET. This study builds on our prior work in which lower LLMZ was associated with lower 6 MWD in youth with PH (7). These pilot data add to our appreciation of musculoskeletal abnormalities in pediatric PH and the potential impact of these deficits on exercise performance. Increased understanding of the peripheral determinants of exercise performance may identify targets for intervention trials.

The general "myopathy" seen in adult PH patients is an area of active investigation, but few studies have examined this issue in pediatric PH. PH is increasingly understood to be a systemic condition with metabolic, inflammatory, genetic, and epigenetic contributions (42). As one of the extra-cardiopulmonary manifestations of this condition, skeletal muscle dysfunction can be grouped into structural deficits, functional impairment, and molecular abnormalities with evidence from both human and animal studies (42). Structural

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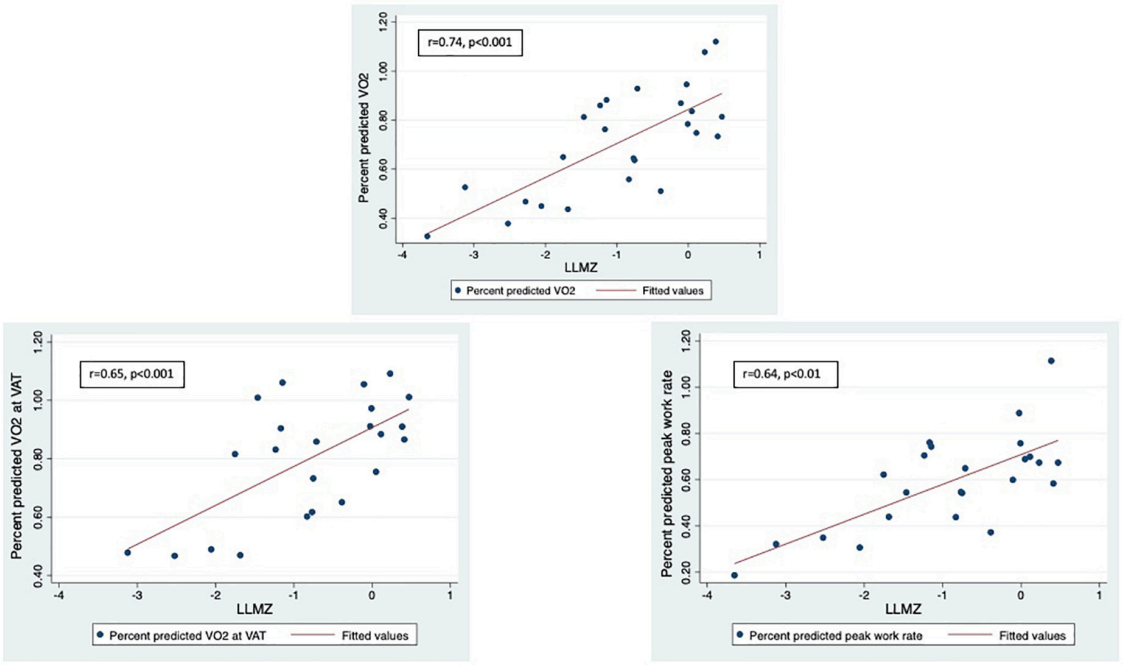

FIGURE 1
LLMZ, D-HGZ, and PAQ score were associated with percent predicted peak VO_2, percent predicted VO_2 at VAT, and percent predicted work. This figure demonstrates the associations between LLMZ and CPET parameters.

deficits include reduced muscle fiber cross sectional area, lower proportion of type I fibers, decreased capillary density, lipid inclusion, and loss of mitochondrial structure (8, 10, 43). Functional impairment can manifest as reduced muscle strength, decreased muscular endurance, impaired oxygenation in the microcirculation, reduced type I fiber tension, and sarcomeric dysfunction (6, 8, 9, 44, 45). Molecular abnormalities have been described including reduced oxidative capacity, increased protein degradation and decreased protein synthesis, impaired angiogenesis, and impaired mitochondrial function (11, 46, 47). The spectrum of muscular abnormalities in children with PH is unknown. As pediatric PH often occurs in the context of congenital heart disease, developmental lung diseases, genetic differences, and other syndromic conditions, the findings may be even more severe. To our knowledge, no other investigators have explored decreased muscle mass and strength in children with PH. The data are essential to understanding the burden of disease across the lifespan and identifying appropriate timepoints for intervention. Future studies should explore the breath of these findings.

We demonstrated associations between muscle deficits and performance on CPET. CPET is a comprehensive assessment of a patient's exercise performance that utilizes inspiratory and expiratory gas exchange to quantify peak oxygen consumption, carbon dioxide production, and minute ventilation (48). Peak VO_2 is the most common indicator of a patient's cardiorespiratory fitness. Adult patients with PH demonstrate decreased peak VO_2, higher VE/VCO_2 (ventilatory equivalents of carbon dioxide) indicating ventilatory inefficiency, lower arterial CO_2 tension and end-tidal CO_2 tension, lower O_2 pulse (VO_2/heart rate, a surrogate for stroke volume), and lower systemic oxygen saturation (49–51). Worse peak VO_2 is associated with more symptoms of dyspnea and fatigue which limit quality of life. Both low peak VO_2 and low 6 MWD are associated with mortality in adults with PAH and are incorporated into REVEAL 2.0 and European Society of Cardiology/European Respiratory Society risk stratification tools (52, 53). However, completion of a CPET requires significant developmental skills and reference values relative to outcomes are lacking in pediatric PH (54, 55). The lack of adverse events in this pilot study suggests that select older children and teenagers with PH can safely perform CPET and eCMR. Peak VO_2 is included in pediatric PAH disease severity guidelines (56) and perhaps exercise parameters will be incorporated into novel pediatric risk stratification tools which are being developed. To our knowledge, this is the first study to express PH participants' CPET performance relative to reference values from more than 1,800 healthy United States children published by members of our study team (28). Participants in our study generally performed at 60–80% predicted, suggesting children with PH already face marked limitations prior to progressive decline in adulthood. Additionally, this is the first report of eCMR in pediatric PH, although we have previously described eCMR in patients

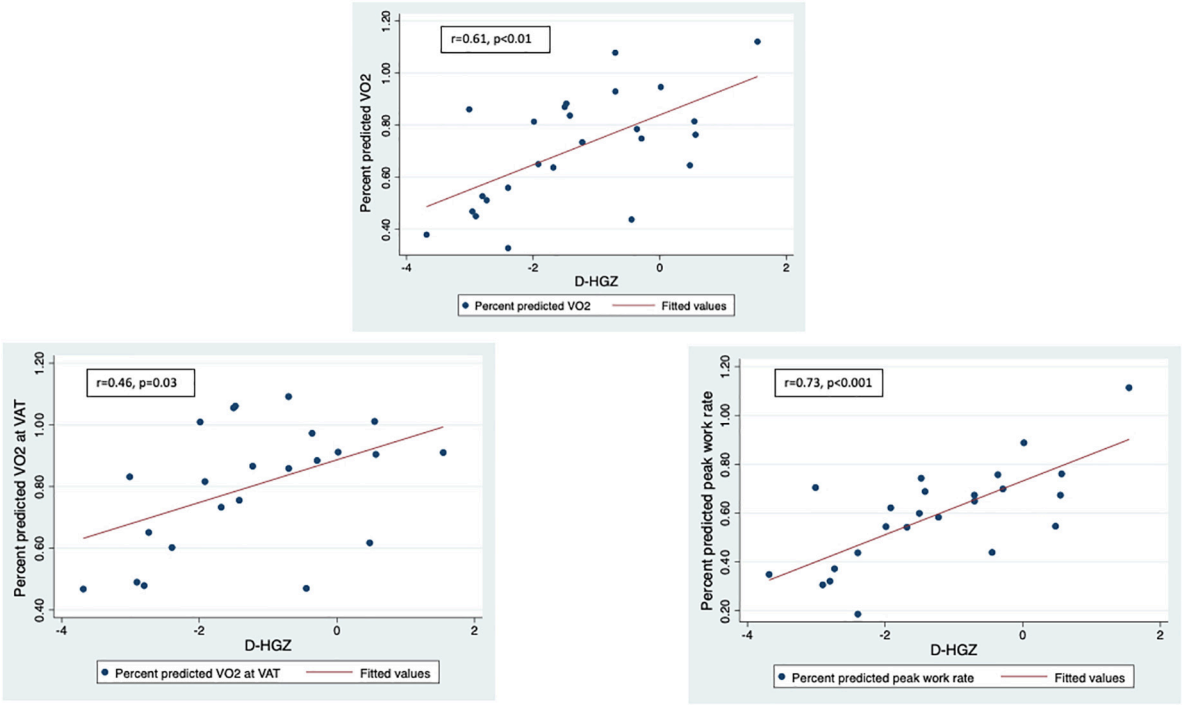

FIGURE 2
LLMZ, D-HGZ, and PAQ score were associated with percent predicted peak VO_2, percent predicted VO_2 at VAT, and percent predicted work. This figure demonstrates the associations between D-HGZ and CPET parameters.

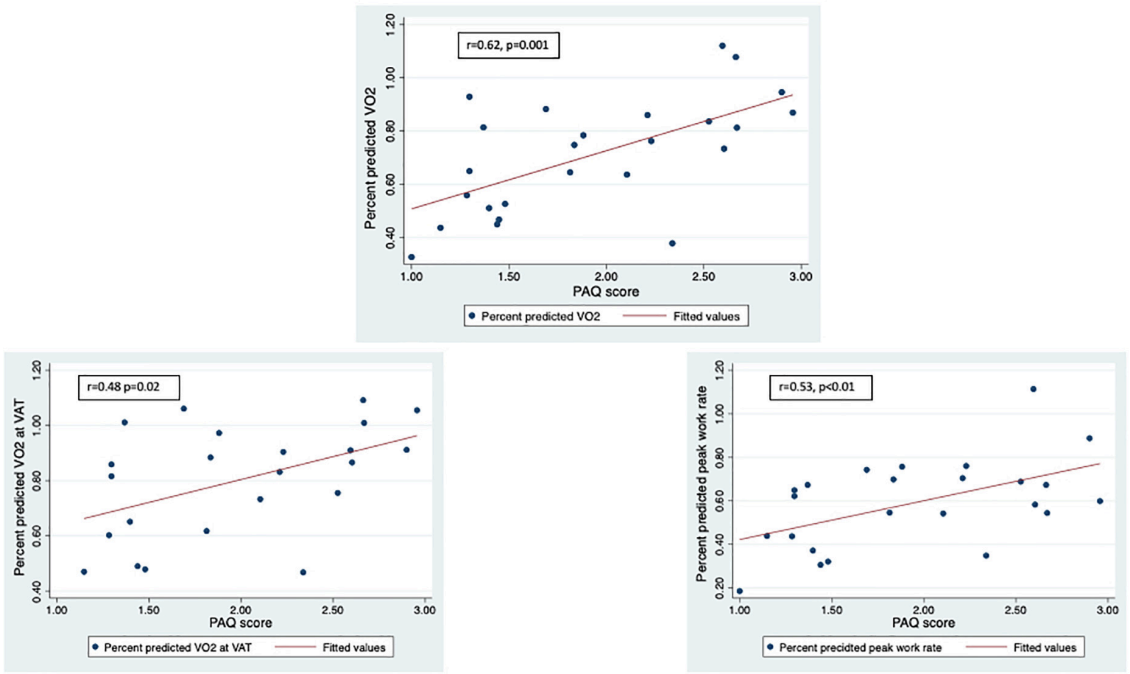

FIGURE 3
LLMZ, D-HGZ, and PAQ score were associated with percent predicted peak VO_2, percent predicted VO_2 at VAT, and percent predicted work. This figure demonstrates the associations between PAQ score and CPET parameters.

TABLE 5 Results from multiple linear regression models testing effect of skeletal muscle and physical activity variables on exercise performance.

Variable	Coefficient	Standard error	95% CI	*P*-value
A. Percent predicted VO_2				
LLMZ	0.07	0.03	0.00, 0.14	0.05
PAQ	0.13	0.05	0.02, 0.23	0.02
D-HGZ	0.05	0.02	−0.01, 0.10	0.09
B. Percent predicted VO_2 at VAT				
LLMZ	0.09	0.5	0.0, 0.19	0.06
PAQ	0.10	0.06	−0.03, 0.23	0.12
D-HGZ	0.02	0.03	−0.04, 0.09	0.52
C. Percent predicted work				
LLMZ	0.05	0.03	−0.02, 0.11	0.16
PAQ	0.10	0.05	0.01, 0.20	0.04
D-HGZ	0.08	0.02	0.03, 0.13	0.003

(A) Model for percent predicted VO_2: $R^2 = 0.63$, $p < 0.001$. (B) Model for percent predicted VO_2 at VAT: $R^2 = 0.42$, $p < 0.01$. (C) Model for percent predicted work: $R^2 = 0.67$, $p < 0.001$.

with single ventricle physiology after Fontan palliation (21). Higher PAQ and handgrip Z-scores were associated with greater change in systemic flow from rest to exercise, raising compelling questions regarding physical activity, strength, and the ability to augment systemic flow on exertion. Future, larger studies should also explore the correlation between eCMR performance and PH disease-specific outcomes.

While peak VO_2 is a common outcome reported in research and clinical care, CPET measures of submaximal performance including VO_2 at VAT and peak work rate relative to respiratory exchange ratio as well as measures of anaerobic strength may better reflect a patient's daily activities and may also be targets for improvement. PH patients rapidly reach anaerobic threshold when performing activities of daily living such as doing laundry and folding clothes, cooking and setting the table, and walking outside with moderate effort (57, 58). These activities are often performed with short bursts of activity. The associations between muscle deficits, VO_2 at VAT, and peak work rate in our study suggest that skeletal muscle deficits may impact everyday activity performance for PH patients and improvements in muscle mass or function could improve quality of life and other outcomes over longer periods. These findings are also consistent with our previous report associating lower LLMZ with lower 6 MWD, another test of submaximal exercise performance (7).

Cardiopulmonary rehabilitation improves symptoms and functional status in adult PH but the mechanisms underlying those improvements are incompletely understood. Some studies have demonstrated improvement in functional status and exercise performance without change in pulmonary hemodynamics. Data such as those from Bauer et al. (6) and Mainguy et al. (10) have supported development of exercise rehabilitation programs to improve muscle function and strength. In a separate study, Mainguy demonstrated increased 6 MWD, increased exercise duration on CPET, and improved VE/CO_2 in association with decreased number of quadriceps type IIx fibers in 5 adult IPAH patients after a 12-week rehabilitation program (59). De Man also demonstrated increased quadriceps strength and endurance, increased quadriceps capillarization, and higher oxidative enzyme activity in 19 adult IPAH patients after a 12-week rehabilitation program (60). There is only one published report of exercise training in pediatric PH. Zöller et al. demonstrated increased treadmill running distance and improved VO_2 at VAT after a 16-week home exercise program in 9 children with PH and functional class I and II (61). Skeletal muscle characterization was not part of that study. While PH patients perform less moderate to vigorous physical activity compared to healthy peers (62), no studies have tested interventions to improve activity. To our knowledge, no pediatric PH exercise trials have described changes in physical activity and/or skeletal muscle performance with training. Future studies should determine whether low skeletal muscle mass is a marker of disease severity or a modifiable determinant of exercise performance in youth with PH. It is not known whether increasing physical activity can augment skeletal muscle characteristics and improve exercise performance in youth with PH.

A primary limitation of this study is the lack of control group. It is not clear whether the relationships between LLMZ, PAQ score, and exercise performance are different in PH patients vs. healthy youth. Additionally, causal inferences cannot be made from these data given the study's cross-sectional design. The small number of participants with certain medication regimens does not allow us to draw conclusions regarding relationships between medications, underlying disease status, and the study outcomes. The relationship between disease progression, muscle deficits, and exercise performance is also unknown. The study was also limited by lack of comparison reference data for lower extremity strength. The lack of association between leg strength and exercise performance may have been because we were unable to express strength relative to gender and body size. Finally, physical activity was measured by self-report. The analyses would have been strengthened by quantification of physical activity by wearable accelerometer. However, despite these limitations, this study has generated preliminary data for future observational studies and interventional trials.

Conclusion

Youth with PH demonstrate inactivity and marked skeletal muscle deficits in association with worse exercise performance on CPET and eCMR. Future studies

should determine whether low skeletal muscle mass is a marker of disease severity or a modifiable target for exercise interventions. Interventions that improve skeletal muscle mass and function could improve exercise performance in this population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Children's Hospital of Philadelphia Institutional Review Board. Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin.

Author contributions

CA designed the study, recruited participants, supervised study procedures, analyzed and interpreted data, and wrote the manuscript. MM and SP supervised exercise testing procedures, interpreted exercise data, and reviewed the final manuscript. MH, KW, and MF supervised exercise cardiac magnetic resonance procedures, analyzed and interpreted the cardiac magnetic resonance data, and reviewed the final manuscript. BZ analyzed and interpreted anthropometry and densitometry data and reviewed the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Angela Bates,
University of Alberta, Canada

REVIEWED BY
Omar R. J. Tamimi,
King Fahad Medical City, Saudi Arabia
Colin McMahon,
University College Dublin, Ireland

*CORRESPONDENCE
Raymond N. Haddad
raymondhaddad@live.com

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Long-term outcomes of transcatheter Potts shunt in children with suprasystemic pulmonary arterial hypertension

Raymond N. Haddad[1]*, Maryline Levy[1,2], Isabelle Szezepanski[1], Sophie Malekzadeh-Milani[1] and Damien Bonnet[1,2]

[1]Centre de Référence Malformations Cardiaques Congénitales Complexes—M3C, Hôpital Universitaire Necker-Enfants Malades, AP-HP, Paris, France, [2]Université de Paris Cité, Paris, France

Background: Transcatheter Potts shunt (TPS) is a palliation alternative for children with severe pulmonary arterial hypertension (PAH). Debates on the long-term outcomes remain unsolved.

Objectives: To evaluate long-term clinical and procedural outcomes of TPS intervention.

Methods: Single-center retrospective data review of children with severe PAH who had TPS between 2009 and 2018. Patients who died perioperatively and early post-procedure were excluded. Long-term outcomes of survivors were evaluated.

Results: Out of 13 identified patients (53.8% males), 7 had endovascular stenting of probe/patent arterial ducts, while 6 individuals had aorta-to-pulmonary radiofrequency perforation and covered stent placement. Compared to baseline, the overall clinical condition significantly improved at discharge ($p < 0.001$) and stayed better at the last visit ($p < 0.05$) despite frequent clinical worsening events across follow-up. Improvement in functional class across follow-up was significant ($p < 0.001$). There was, however, no significant improvement in other disease markers (TPASE, 6MWD z-scores, and NT-proBNP levels) or reduction in PAH medications. The median follow-up was 77.4 months (IQR, 70.7–113.4). Survival was 100% at 1 year and 92.3% at 6 years. Freedom from reinterventions was 77% at 1 year and 21% at 6 years. Nine (69.2%) patients had stent reinterventions at a median of 25 months (IQR, 9.5–56) postoperative. Balloon dilatation and restenting were performed in 53.8% and 46.2% of patients, respectively. High-pressure post-dilatation of implanted stents was performed in 53.8% of patients during TPS intervention for incomplete stent expansion and/or residual pressure gradient and was associated with higher rates of reinterventions ($p = 0.021$). Stent malfunctioning was present in 46.2% of patients at last follow-up. Two patients are listed for heart-lung transplantation.

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Conclusion: Survivors of TPS procedures experience significant improvement in functional class that can be durable. Clinical worsening and stent malfunctioning are frequent morbid events indicating recurrent transcatheter reinterventions throughout follow-up. Six-year survival is, however, satisfactory.

KEYWORDS

children, heart failure, outcomes, Potts shunt, pulmonary arterial hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a chronic disease and the prognosis remains guarded despite profound advances in medical therapies (1, 2). The revival of the surgical Potts shunt as palliation of PAH in children was an interesting innovation coming from collaborative research in Paris hospitals (3–5). The outcomes of this surgical procedure were promising inspiring interventionists to duplicate the technique using transcatheter technologies (6, 7). Transcatheter Potts shunt (TPS) was initially performed by stenting a restrictive arterial duct with effective results (6, 8). However, in the absence of an arterial duct, the *de novo* percutaneous shunt creation between the left pulmonary artery (LPA) and descending aorta (DAO) was technically challenging and not complication-free (7, 9). The technical aspects and early outcomes of both procedures were described in several studies (6–9). Early morbidity and mortality benefits were reported but these conclusions were mainly derived from studies of mixed populations with surgical and transcatheter shunts, keeping debates regarding TPS ongoing (2, 10, 11). The international Potts shunt registry recently underscored that TPS was a risk factor for early mortality (12). The data of this registry also showed that the type of shunt, and in particular transcatheter shunts, did not prove a significant risk factor for late events. The technical issues of TPS, in the long run, were not addressed in the registry study. Therefore, we expand upon these earlier findings to evaluate the long-term outcomes of a large single-center experience with TPS and focus on the durability of the implanted stents in procedure survivors.

Patients and methods

Study design

We retrospectively reviewed and included all children with suprasystemic PAH who survived ductal and non-ductal TPS procedures at our institution from October 2009 to June 2018. All patients were assigned to group 1 according to the classification of World Symposium on Pulmonary Hypertension (WSPH). Four patients had non-ductal TPS procedures and died either per-operatively, in-hospital, or within 4 weeks after hospital discharge. These patients have been reported in previous cohorts and were excluded from this study (7, 9, 13). They had pre-operative World Health Organization functional class (WHO-FC) IV with severe right ventricular systolic dysfunction requiring elective or rescue veno-arterial ECMO support.

All children had detailed investigations and received supportive therapy including diuretics, oral anticoagulation, and oxygen on a case-by-case basis. Pre-operative demographics, invasive hemodynamics, and procedural data were collected from the medical records, and catheterization reports. We specifically collected WHO-FC, presence of syncope, upper and lower limb oxygen saturations, 6-min walk distance (6MWD) values and z-scores (14), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, Tricuspid Annular Plane Systolic Excursion (TAPSE) values and z-scores (15), maximal velocity on implanted stents, number, dose, and type of PAH specific medical therapies at baseline, hospital discharge, 6 and 12 months follow-up and last available follow-up to be evaluated and compared. Specific PAH therapies including oral endothelin receptor antagonists (ERA), phosphodiesterase type-5 inhibitors (PDE5I), and subcutaneous or intravenous prostanoid therapy were used either as sequential add-on therapy or as up-front triple therapy according to clinical status at baseline and worsening events during the follow-up.

Procedure

All patients underwent repetitive pre-operative detailed clinical and echocardiographic evaluations. Candidates for TPS were children with supra-systemic PAH, non-responder during acute vasoreactivity testing, along with worsening WHO-FC, and/or insufficient improvement in clinical signs and symptoms despite maximal doses of at least a combination of PDE5I and ERA for at least 6 months before the TPS procedure. Patients with one PAH therapy and immediately sent for TPS had restrictive arterial ducts and presented special socioeconomic

Abbreviations: DAO, descending aorta; ERA, endothelin receptor antagonists; IQR, interquartile; LPA, left pulmonary artery; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5I, phosphodiesterase type-5 inhibitors; TAPSE, tricuspid Annular Plane Systolic Excursion; TPS, Transcatheter Potts shunt; WHO-FC, World Health Organization functional class; 6MWD, 6-min walk distance.

conditions (i.e., living abroad, family decision) motivating the earlier indication for TPS. The Potts shunts created in the catheterization laboratory included: (1) endovascular stenting of a restrictive or probe arterial duct (i.e., ductal TPS); and (2) *de novo* shunt generation between the LPA and the DAO with a direct radiofrequency puncture and subsequent placement of a balloon-expandable covered stent (i.e., non-ductal TPS). Both TPS procedures were previously detailed (6, 7). In case of incomplete stent expansion and/or residual pressure gradient > 10 mmHg across the stent, stent re-dilation was performed using appropriately sized angioplasty high-pressure balloons to reduce or abolish the pressure gradient. Patients who had ductal stenting were prescribed single antiplatelet therapy while those who had non-ductal TPS were prescribed dual antiplatelet therapy with aspirin and clopidogrel. Patients were transferred to the ICU for close monitoring when indicated.

Follow-up protocol

Routine outpatient follow-ups were scheduled for 1, 3, 6, and 12 months post-procedure and yearly thereafter. Assessment included clinical evaluation of clinical status, physical examination (with a focus on clinical signs of right ventricular failure), saturation measurements, transthoracic echocardiography, lab tests, and 6MWD test. Improvement in WHO-FC, shunting across the Potts shunt, quantitative improvement in right ventricular function (i.e., increase in TAPSE scores), and decrease in NT-proBNP levels were used as criteria to modify the PAH medical therapies during follow-up. We defined clinical worsening by the presence of at least one of the following criteria: (1) worsening WHO-FC; (2) rising NT-pro BNP levels ≥ 1,400 pg/mL; (3) decreasing TAPSE score ≤ 15 mm; (4) dose increase or adjunction of diuretics; and (5) adjunction of new PAH-specific medical therapy. Patients were classified in a good overall clinical condition in the absence of any aspect of clinical worsening or lack of improvement. We defined stent malfunctioning as Doppler maximum velocity on the implanted stent > 2 m/s. Follow-up cardiac catheterization (hemodynamic and/or interventional) was performed in case of documented stent malfunctioning and/or clinical worsening. Percutaneous interventions on the stent included balloon dilation and endovascular re-stenting and were performed in case of a significant invasive pressure gradient (i.e., ≥ 10 mmHg) (7). Stent fracture and degree of neo-intimal proliferation were also looked at.

Statistical analyses

Statistical analyses were performed using SPSS, Version 22.0 for Macintosh (IBM, Armonk, NY, USA). Categorical variables were reported as frequency and percentage and continuous variables were represented as median with interquartile range. Statistical analysis for categorical variables was conducted using Fisher's exact test. Distribution of continuous variables was compared using Mann Whitney *U*-test. A p-value < 0.05 was considered statistically significant. All reported p-values are two-sided. Kaplan-Meier univariate analyses were generated to show event-free rates.

Results

Baseline patients characteristics

We identified 13 children (53.8% males) discharged alive after TPS. Patient characteristics are shown in **Table 1**. The median age and weight at the time of the intervention were 8.7 years (IQR, 5.7–12) and 26.8 kg (IQR, 18–34.7), respectively. The median time from PAH diagnosis to TPS was 2.5 years (IQR, 1.4–5.8). All children had asthenia and growth retardation. At the time of the procedure, 54% of patients were receiving triple therapy, 23% dual therapy, and 23% monotherapy. More specifically, 92.3% of children were receiving a PDE5I, 84.6% were receiving an ERA, and 53.8% were receiving either intravenous or subcutaneous infusions of prostanoids. When referred for the TPS procedure, 69.2% of the children were considered WHO-FC III or IV. Pre-operative right heart catheterization documented supra-systemic right ventricular pressures in all patients (**Table 1**).

Procedure

At the time of the procedure, all children were outpatients. Seven children had ductal TPS (median age, 8.1 years) and 6 children had non-ductal TPS (median age, 9.8 years). The baseline procedural data are shown in **Table 1**. All implanted stents were pre-mounted on single delivery balloons. LIFESTREAM® stent (Bard Peripheral Vascular, Inc., Tempe, AZ, USA) was implanted in 46.2% of patients and was more frequently used in ductal TPS procedures. Of all implanted stents, 92.3% were made of stainless steel, 92.3% had an open-cell design, and 61.5% were PTFE-covered stents. The median nominal diameter of stents was 7 mm (IQR, 7–8.5). Implanted stents were post-dilated using high-pressure balloons in 7 (53.8%) patients to eliminate residual pressure gradient and achieve the target diameter. Post-dilation balloons were larger than stents' delivery balloons by a median of 2 mm (IQR, 1–3.5). The median TPS final angiographic diameter was 8 mm (IQR, 6.7–8.7) and the median value of the shunt-to-DAO diameter ratio was 0.65 (IQR, 0.57–0.77). Three stents were protruding in the aorta without a significant gradient across the aortic isthmus. A slight waist in mid-stent was persistent in 6 (46.2%) patients at the end of the intervention. Five patients were transferred

TABLE 1 Baseline clinical and procedural characteristics.

	Total, $n = 13$	Group 1, $n = 6$	Group 2, $n = 7$	*P-value*
Male, *N* (%)	7 (53.8)	3 (50)	4 (57.1)	1[a]
Demographics at diagnosis				
Age (years), *median (IQR)*	3.67 (0.79, 9.75)	6.29 (2.08, 11.44)	2.58 (0.67, 5.75)	0.445[b]
Weight (Kg), *median (IQR)*	14.7 (6.9, 22.5)	18.5 (10.6, 34.25)	13 (6.7, 21)	0.534[b]
Oxygen saturation (%), *median (IQR)*	96 (91.5, 97.5)	96.5 (95.5, 98.5)	93 (89, 97)	0.138[b]
Cyanosis, *N* (%)	3 (23.1)	–	3 (42.9)	0.192[b]
Neurological comorbidity, *N* (%)	4 (30.8)	3 (50)	1 (14.3)	0.07[a]
Associated hemodynamically significant CHD, *N* (%)	4 (30.8)	–	4 (57.1)	0.192[a]
Idiopathic pulmonary arterial hypertension, *N* (%)	4 (30.8)	2 (33.3)	3 (28.6)	1[a]
Heritable pulmonary arterial hypertension, *N* (%)	7 (53.8)	4 (66.7)	3 (42.9)	0.592[a]
BMPR2 mutation, *N* (%)	4 (30.8)	4 (66.7)	–	**0.021**[a]
TBX4 mutation, *N* (%)	1 (7.7)	–	1 (14.3)	–
Down syndrome, *N* (%)	2 (15.4)	–	2 (28.6)	0.462[a]
Delay from diagnosis to intervention (years), *median (IQR)*	2.49 (1.45, 5.83)	5.06 (2.41, 6.71)	1.88 (0.7, 4.99)	0.138[b]
Demographics at intervention, *median (IQR)*				
Age (years)	8.67 (5.66, 12)	9.83 (8.67, 14.39)	8.08 (2.25, 9.67)	0.101[b]
Weight (kg)	26.8 (18, 34.7)	34.5 (26.35, 47.1)	22 (12.5, 31)	**0.022**[b]
Height (cm)	133 (108, 140.5)	134.5 (130, 148)	122 (88, 140)	0.181[b]
BSA (m^2)	0.97 (0.72, 1.17)	1.16 (0.96, 1.38)	0.84 (0.55, 1.08)	**0.022**[b]
Baseline catheterization data, *median (IQR)*				
Mean right atrium pressure (mmHg)	9 (6, 11)	9 (6.5, 9.5)	8.5 (5.7, 11.2)	0.662[b]
Systolic pulmonary artery pressure (mmHg)	113 (90, 132.5)	97 (87.7, 132)	120 (89, 134)	0.534[b]
Mean pulmonary artery pressure (mmHg)	83 (61.5, 82.5)	68 (52.2, 86.2)	87 (64, 100)	0.138[b]
Pulmonary artery-to-aorta gradient (mmHg)	1.23 (1.1, 1.39)	1.17 (1.09, 1.54)	1.26 (1.17, 1.39)	0.945[b]
Index PVR (Wood units/m^2)	21 (13.57, 26.23)	17.6 (11.9, 26.2)	22.4 (19.2, 30.32)	0.352[b]
Cardiac Index (L/min/m^2)	3.2 (2.5, 4.4)	3.02 (2.4, 3.9)	3.65 (2.3, 5.2)	0.537[b]
DAO to LPA distance (mm)*, *median (IQR)*	–	2.1 (0, 3.5)	–	–
Type of implanted stents, *N* (%)				
LIFESTREAM (Bard)	6 (46.2)	5 (83.3)	1 (14.3)	**0.029**[a]
Other stents	7 (53.8)	1 (16.7)	6 (85.7)	
VALEO Lifestent (Bard)	4	–	4	
Atrium V12 (Maquet)	1	–	1	
BeGRAFT (Bentley)	1	1	–	
Palmaz Genesis (Cordis)	1	–	1	
Stent nominal diameter (mm), *median (IQR)*	7 (7, 8.5)	7 (7, 7.75)	8 (7, 9)	0.534[b]
Stent length (mm), *median (IQR)*	26 (19.5, 26)	26 (21.2, 36.5)	26 (18, 26)	0.445[b]
High-pressure stent dilation *N* (%)	7 (53.8)	4 (66.7)	3 (42.9)	0.592[a]
Final shunt diameter* (mm), *median (IQR)*	8 (6.7, 8.7)	8.53 (6.9, 8.9)	8 (6.5, 8.1)	0.295[b]
DAO diameter* (mm), *median (IQR)*	12.2 (10, 12.9)	12.2 (11.6, 13.4)	10 (9.8, 12.9)	0.366[b]
Shunt-to-DAO diameter ratio, *median (IQR)*	0.65 (0.57, 0.77)	0.64 (0.57, 0.74)	0.65 (0.57, 0.83)	0.836[b]
Angle between stent and DAO (degrees)*, *median (IQR)*	104 (90, 120)	104 (90, 115)	106 (85, 121)	1[b]
Persistent waist in mid-stent, *N* (%)	6 (46.2)	3 (50)	3 (42.9)	1[a]
Post-procedural PA-to-aorta gradient (mmHg), *median (IQR)*	2 (0, 10)	1 (0, 12.5)	2 (2, 10)	0.534[b]
Intensive care unit stay (days), *median (IQR)*	0 (0, 3)	2.5 (0, 4.25)	0 (0, 0)	0.101[b]

Group 1, non-ductal transcatheter Potts shunt; Group 2: ductal transcatheter Potts shunt. BSA, body surface area; DAO, Descending Aorta; LPA, left pulmonary artery; PA, pulmonary artery; PVR, pulmonary vascular resistance. *Measured in right anterior oblique RAO projection. [a]Fisher Exact test; [b]Mann-Whitney *U*-test. Bold values are significant *p*-values.

to the ICU for postoperative management. Median ICU stay of children with TPS creation was 2.5 days (IQR, 0–4.2 days).

Immediate and short-term follow-up

All children were uneventfully discharged home with significant improvement in the overall clinical condition that was classified as good in all patients. At discharge, 92.3% of children were considered WHO-FC I or II. The median upper limb/lower limb rest saturation gradient at the time of discharge was 9% (IQR, 6.5–17%). Of the seven patients receiving prostanoid therapy before the procedure, 2 were weaned by hospital discharge, 1 at 3 months, and 1 at 6 months post-procedure.

Long-term follow-up

The median follow-up was 77.4 months (IQR, 70.7–113.4). Detailed comparison of clinical, echocardiographic, biological, and pharmacological parameters across follow-up is outlined in **Table 2**. One 4-year-old patient with ductal TPS died 28.5 months post-procedure from a severe respiratory syncytial virus infection. The overall survival rate was 92.3% at 6 years (**Figure 1**). The left ventricular function and cardiac output were initially improved and preserved during follow-up. All children caught up to normal growth curves. There was no recurrence of syncope in the 4 patients who experienced syncope before TPS. Two out of nine patients who did not have syncopal episodes in the past, experienced syncope during follow-up.

The remarkable improvement in the baseline overall clinical condition of discharged patients was inconsistent and variable across follow-up (**Figure 2**). Patients experienced frequent clinical worsening events that were concurrent with stent malfunctioning as detected on ultrasound. Despite this variability in clinical condition, the overall improvement remained significant at the last follow-up when compared to baseline status ($p < 0.025$), and discharge status ($p = 0.05$) (**Figure 2**). More specifically, improvement in functional status across follow-up was significant ($p < 0.001$). At the last visit, three patients were WHO-FC I, nine patients were WHO-FC II, and one patient was WHO-FC III. When compared with preoperative values, serum NT-proBNP levels diminished from a median of 170 pg/mL (IQR, 141–609) to a median of 145.5 pg/mL (IQR, 27.2–259.7) at last visit but this decrease was not significant ($p = 0.118$). At the last visit, the median 6MWD values and z-scores were not significantly improved when compared with preoperative data. Distribution of TAPSE z-scores across follow-up was also not significant (**Table 2**). At the last visit, 4/13 (30.8%) patients (2 with non-ductal TPS and 2 with ductal TPS) were receiving triple combination therapy. Weaning of prostanoid therapy weaning was not possible in two patients (one with non-ductal TPS and one with ductal stenting). Prostanoid therapy was stably weaned in 4 patients with non-ductal TPS. It was also weaned in one patient 2 months after non-ductal TPS and then restarted after 52 months for progressive clinical worsening and severe stent malfunctioning. Finally, prostanoid therapy was *de novo* started in another patient 82.8 months after ductal TPS for clinical worsening without stent malfunctioning. Reduction in overall use of PAH-specific medications was not significant.

Transcatheter reinterventions

The final procedural outcomes are shown in **Table 3**. The freedom from transcatheter reinterventions was 77% at 1 year and 21% at 6 years (**Figure 3**). Three patients did not require any redo cardiac catheterization (hemodynamic or interventional) on a follow-up of 28.5, 52, and 77.4 months, respectively. These 3 patients had early ductal TPS (within 2 years of PAH diagnosis) and did not require high-pressure post-dilation of implanted stents during the ductal TPS intervention. Of these three patients, two were in the latter half of the cohort (**Figure 4**). One patient with non-ductal TPS had one diagnostic hemodynamic redo cardiac catheterization 6 months postoperative for a protruding stent in the aorta and did not require any reintervention. The remaining 9/13 (69.2%) patients had transcatheter reinterventions on implanted stents at a median of 25 months (IQR, 9.5–56) postoperative. These nine patients had a median of 2 (range, 1–3) transcatheter reinterventions per patient. Stent balloon dilatations were performed in 7/13 (53.8%) patients at a median of 25 months (IQR 8–59) postoperative. Endovascular implantations of a second stent were performed in 6/13 (46.1%) patients at a median of 41 months (IQR 24–68) postoperative. We did not identify any stent fracture on follow-up redo catheterizations. Intimal proliferation was noted in two patients. At the latest follow-up, stent malfunctioning was present in 6/13 (46.2%) patients of which 3 had non-ductal TPS. In 2/3 patients with malfunctioning non-ductal TPS, the stent was severely damaged (infolded/distorted geometry) after repetitive transcatheter reinterventions. Interventional therapy was not considered beneficial and both patients are listed for heart-lung transplantation for almost 2 years. Univariate analysis identified that high-pressure post-dilatation of implanted stents during the TPS intervention was alone associated with higher rates of reinterventions ($p = 0.021$). The need for reinterventions was quite similar in both techniques applied for TPS (**Table 4**).

Discussion

Despite technical challenges, the spatial proximity between the DAO and LPA made the creation of the Potts shunt possible

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TABLE 2 Detailed comparison of clinical, echocardiographic, biological, and pharmacological parameters across follow-up.

	Baseline, *n* = 13	Discharge, *n* = 13	6 months follow-up, *n* = 12	12 months follow-up, *n* = 13	Latest follow-up, *n* = 13	*P-value*	*P-value*‡
Weight (Kg), *median (IQR)*	26.8 (18, 34.7)	26.8 (18, 34.7)	30.5 (22.4, 36.8)	35.1 (24.8, 40.9)	44 (35.9, 53.4)	**0.022**[a]	**0.005**[a]
I-II, *N* (%)	4 (30.8)	12 (92.3)	10 (83.3)	13 (100)	12 (92.3)	**<0.001**[b]	**0.004**[b]
III-IV, *N* (%)	9 (69.2)	1 (7.7)	2 (16.7)	–	1 (7.7)		
Syncope, *N* (%)	4 (30.8)	–	2 (16.7)	–	2 (15.4)	0.363[b]	0.645[b]
UL oxygen saturation (%), *median (IQR)*	97 (94, 98.5)	98 (96, 99.5)	96 (94.2, 99)	97 (95, 98)	96 (93.5, 98.5)	0.757[a]	0.614[a]
UL/LL oxygen saturation gradient, *median (IQR)*	N/A	9 (6.5, 17)	9.5 (2.7, 18.2)	4 (1, 14.5)	11 (4.5, 15)	0.25[a]	–
TAPSE (mm), *median (IQR)*	18 (12.1, 23)	19 (17, 23.5)	22 (19.3, 23.7)	19.5 (16.5, 21.6)	20.5 (18, 25.7)	0.225[a]	0.06[a]
TAPSE z-score, *median (IQR)*	−0.77 (−3.59, 1.87)	−0.77 (−1.53, 1.59)	0.28 (−1.16, 2.59)	−0.91 (−1.69, 0.98)	−0.47 (−2.92, 0.7)	0.506[a]	0.979[a]
Maximum velocity on stent (m/s), *median (IQR)*	N/A	1.5 (1.5, 2)	2 (1.5, 2.2)	2 (1.6, 2.8)	2 (1.6, 2.3)	0.358[a]	–
NT-pro BNP level (pg/ml), *median (IQR)*	170 (141, 609)	I/D	130 (57.7, 255.2)	59.5 (20.5, 205)	145.5 (27.2, 259.7)	0.112[a]	0.118[a]
6MWT* (m), *median (IQR)*	448 (328.5, 495.3)	451 (355.3, 487)	425 (398, 637)	449 (354, 540)	407 (319, 460)	0.701[a]	0.468[a]
6MWT z-score, *median (IQR)*	−3.69 (−4.65, −2.26)	−3.4 (−4.68, −2.55)	−2.47 (−4.25, −0.13)	−3.73(−4.8, −2.06)	−4.63(−5.71, −4.29)	0.121[a]	0.072[a]
Number of pulmonary hypertension therapies, *median (IQR)*	3 (1.5, 3)	2 (1.5, 3)	2 (2, 2)	2 (2, 2)	2 (2, 3)	0.715[a]	0.545[a]
Type-5 phosphodiesterase (PDE5) inhibitor, *N* (%)	12 (92.3)	11 (84.6)	11 (91.7)	12 (92.3)	12 (92.3)	1[b]	1[b]
Sildenafil total dose (mg/day), *median (IQR)*	60 (35, 60)	60 (50, 60)	60 (55, 60)	60 (57.5, 60)	60 (60, 60)		
Dose adjusted to weight (mg/Kg/day), *median (IQR)*	1.98 (1.71, 2.4)	2.03 (1.71, 2.73)	2.31 (1.73, 3.36)	1.83 (1.55, 2.51)	1.5 (1.25, 1.62)		
Tadalafil total dose (mg/day), *median (IQR)*	–	–	30 (20, –)	40 (40, 40)	40 (40, 40)		
Dose adjusted to weight (mg/Kg/day), *median (IQR)*	–	–	0.62 (0.25, –)	0.74 (0.51, –)	0.56 (0.37, 0.61)		
Endothelin receptor antagonist (ERA), *N* (%)	11 (84.6)	10 (76.9)	11 (91.7)	11 (84.6)	12 (92.3)	0.984[b]	1[b]
Total dose (mg/day), *median (IQR)*	125 (80, 160)	126.5 (92, 168)	125 (80, 128)	128 (96, 160)	173.7 (102.1, 192)		
Dose adjusted to weight (mg/Kg/day), *median (IQR)*	3.68 (3.21, 4.35)	4.01 (3.53, 4.56)	3.69 (3.57, 4.49)	3.97 (3.6, 4.2)	3.88 (3.16, 4.28)		
Prostanoid therapy, *N* (%)	7 (53.8)	5 (38.5)	2 (16.7)	2 (15.4)	4 (30.8)	0.109[b]	0.428[b]
Epoprostinol	3 (42.9)	2 (40)	–	–	–		
Treprostinil	4 (57.1)	3 (60)	1 (50)	1 (50)	1 (25)		
Dose (ng/kg/min)	31 (20, 37.5)	23 (14.7, 31)	35[#]	36.3[#]	32[#]		
Selexipag	–	–	1 (50)	1 (50)	3 (75)		
Dose (μg/day)	–	–	400[#]	2400[#]	2800 (2400, 3000)		
Diuretic therapy	–	–	–	2 (15.4)	2 (15.4)		

[a]Kruskal-Wallis test. [b]Fisher Exact test. LL, Lower limb; TAPSE, Tricuspid annular plane systolic excursion; UL, upper limb; WHO, world health organization- Functional class; 6MWT, 6 min walking test; N/A, not applicable; I/D, insufficient data. ‡Comparison of baseline to last follow-up. *Due to age, the 6MWT could not be performed initially and during follow-up in all patients. [#]Single value. Bold values are significant *p*-values.

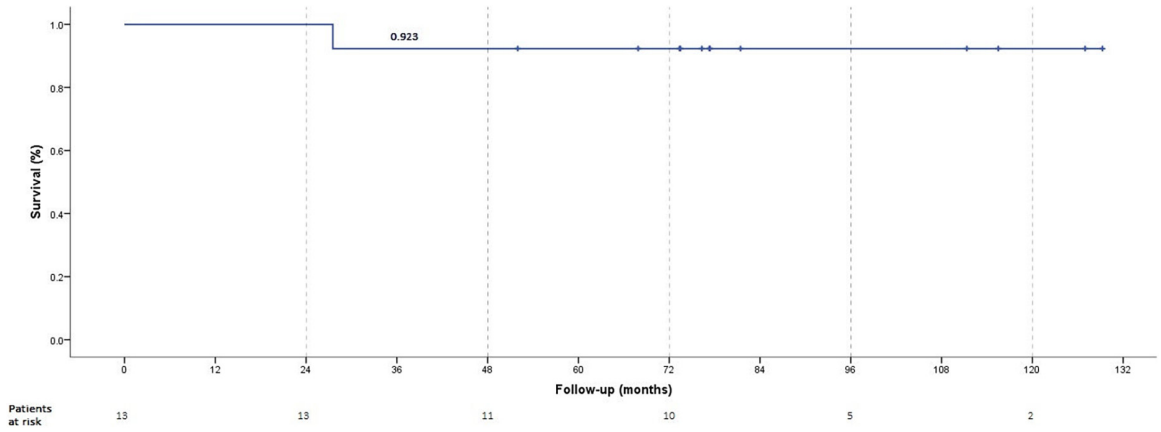

FIGURE 1
One to 6 years survival rates.

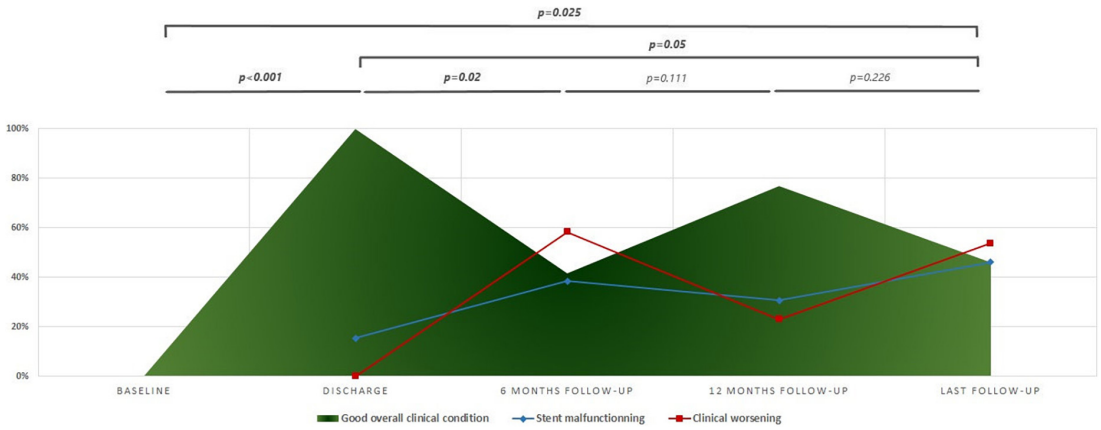

FIGURE 2
Progression of overall clinical status across follow-up. The clinical worsening is defined by the presence of at least one of the following: (1) worsening in world health organization- Functional class (WHO-FC); (2) NT-pro BNP $\geq$ 1,400 pg/ml; (3) tricuspid annular plane systolic excursion (TAPSE) $\leq$ 15 mm; (4) increase or adjunction of diuretics; and (5) adjunction of new pulmonary arterial hypertension (PAH) specific medical therapy. Stent malfunctioning is defined as maximum velocity on stent $>$ 2 m/s.

using transcatheter techniques (7, 16–20). This approach was easily performed in the presence of a tiny arterial duct (5, 6). However, the limitations related to the design, delivery profile, size portfolio, and endurance of available stents are now identified as impediments to the long-term durability of early positive procedural outcomes. The choice of initial stent diameter was based on an aggregate consideration of the patient's age and weight, surgical target diameter, and narrowest arterial duct diameter limiting the straightforward implantation of an adequately sized stent (5, 6, 21). Therefore, we had to gradually enlarge implanted stents by sequential and repetitive balloon inflations to match patients' growth and disease progression. This technique was somehow helpful in maintaining pulmonary blood flow and limiting lower limb desaturation. However, it appears to be associated with higher rates of reinterventions when theoretically compared to the surgical Potts (4, 5, 10, 11).

The non-ductal TPS required the actual creation of a bridged connection between two distant vessels. The shape of the tightest contact area and the distance between the LPA and DAO were both variable. The absence of dedicated material for this application made the procedure technically challenging and risky (7, 9, 16, 17). The implanted covered vascular stents were not available in all combinations of diameters and lengths for a tailored procedure. Using a covered stent of appropriate diameter resulted in having a stent protruding too much into the aorta, as we experienced in three patients. Sequential stent re-dilation using appropriately sized high-pressure angioplasty balloons was also necessary in other seven patients to first achieve the desired diameter and eliminate the mid-stent waist

TABLE 3 Final procedural outcomes.

Follow-up (months), *median (IQR)*	77.4 (70.7, 113.4)
Stent malfunctioning at latest follow-up*, *N* (%)	6 (46.2)
Stent protrusion in the aorta (without hemodynamical significance), *N* (%)	3 (23.1)
Stent fracture, *N* (%)	–
Stent intimal proliferation, *N* (%)	2 (15.4)
Re-catheterizations, *N* (%)	10 (76.9)
Number of re-catheterizations per patient, *median (total range)*	2 (0–4)
Control hemodynamic re-catheterizations, *N* (%)	6 (46.1)
Transcatheter re-interventions, *N* (%)	9 (69.2)
Time to first re-intervention (months), *median (IQR)*	25 (9.5, 56)
Number of re-intervention per patient, *median (total range), n = 9*	2 (1–3)
Stent balloon dilatation, *N* (%)	7 (53.8)
Time to balloon dilatation (months), *median (IQR)*	25 (8, 59)
Re-stenting, *N* (%)	6 (46.2)
Time to re-stenting (months), *median (IQR)*	41 (24, 68)
Listed for heart-lung transplantation, *N* (%)	2 (15.4)
Late death, *N* (%)	1 (7.7)

*Defined as maximum velocity on stent > 2 m/s.

within the relatively rigid vessel arterial walls, and secondly to abolish the residual pressure gradient (19, 22).

The survival rate in this cohort was better than the one reported in the international Potts registry for the patients discharged home and this can be simply explained by the different design of the two studies and the inclusion criteria of patients (12). The analysis of registry data showed that non-ductal TPS was a risk factor for early mortality but did not identify transcatheter shunts as a significant risk factor for late death or lung transplantation (12). Here, we particularly questioned the durability of the implanted stents during ductal and non-ductal TPS. The most important finding was that the outstanding improvement in overall clinical condition at discharge was variable across follow-up and weaning of prostanoid therapy was not possible in all survivors. This is not the case in survivors of surgical Potts shunts where immediate clinical improvement in survivors is long-lasting and allows progressive weaning of prostanoid therapy as reported elsewhere (4, 5). This finding was not quite surprising since stent malfunctioning was expected as frequently reported in other interventions implicating endovascular stent implantations (22, 23). The aforementioned challenging anatomical conditions of stent implantation during TPS procedure are even additional risk factors for higher rates of stent malfunctioning events.

Debates, learning points, and room for improvements

Debates on prostanoid therapy and future transplantation candidacy in patients with Potts shunt have been discussed elsewhere (10–12, 24, 25). Three issues are worth debating today.

Is there a learning curve impact?

Procedure-related complications and long-term morbidity did not appear consistently less in the latter part of our center experience (**Figure 4**). Indeed, it was not expected because there was no important change in the implantation techniques and the portfolio limitations of the implanted pre-mounted stents were existent all across the observation period.

Should we abandon the transcatheter Potts shunt procedure?

Putting the study findings into perspective, we might conclude that TPS is a bad idea because the need for reinterventions did not vary significantly with the applied technique for TPS. However, we cannot ignore that in-hospital mortality has been solely associated with non-ductal TPS when compared to surgical Potts and ductal TPS in the international Potts registry (12). Aortic stent protrusion

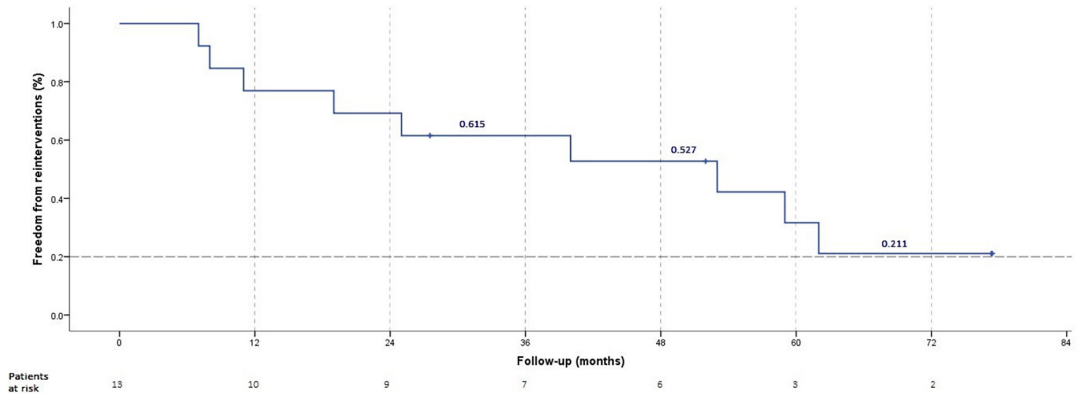

FIGURE 3
Freedom from re-intervention.

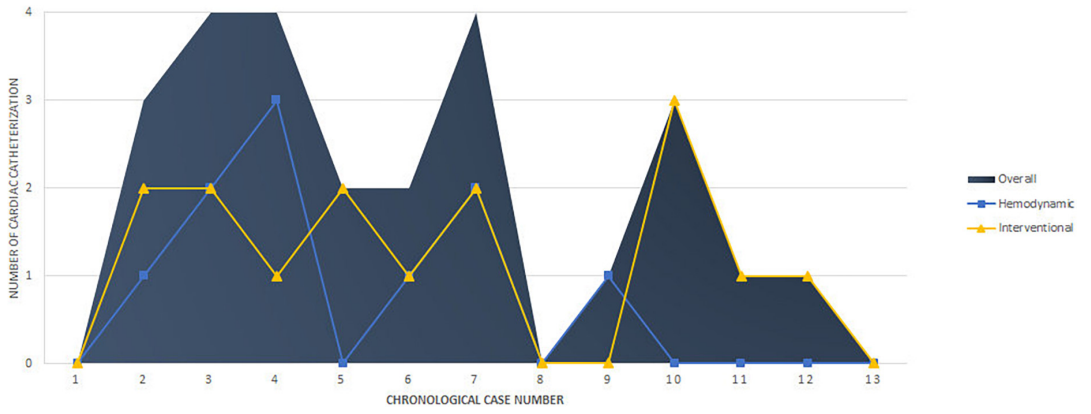

FIGURE 4
Number and type of re-catheterization according to chronological case number.

TABLE 4 Distribution of study parameters according to the need for reinterventions.

	Re-intervention		*P-value*
	No	**Yes**	
Male gender	2 (50)	5 (55.6)	1[a]
Demographics at intervention			
Delay from diagnosis (years)	1.45 (0.65, 3.79)	4.99 (2.28, 7.47)	0.076[b]
Age (years)	5.46 (2, 12.91)	8.92 (8.37, 12)	0.33[b]
Weight (Kg)	23.5 (10.5, 36.2)	26.8 (23.3, 34.5)	0.71[b]
Height (cm)	109 (80, 138)	134 (125, 142)	0.26[b]
Intervention type			
Non-ductal transcatheter Potts shunt	1 (25)	5 (55.6)	0.559[a]
Ductal transcatheter Potts shunt	3 (75)	4 (44.4)	
Stent nominal diameter	8 (6.5, 9.5)	7 (7, 8)	0.503[b]
Stent length	23 (18, 35)	26 (22, 26)	0.825[b]
Type of implanted stents			
Lifestream	2 (50)	4 (44.4)	1[a]
Other stents	2 (50)	5 (55.6)	
High-pressure balloon post-dilatation	–	7 (77.8)	**0.021**[a]
Persistent waist in mid-stent, *N* (%)	2 (50)	4 (44.4)	1[a]
Final shunt diameter (mm), *median (IQR)*	8 (6.3, 8.6)	8 (6.7, 9)	0.825[b]
Shunt-to-DAO diameter ration, *median (IQR)*	0.83 (0.64, 0.83)	0.59 (0.55, 0.67)	0.076[b]
Angle between stent and DAO (degrees), *median (IQR)*	120 (98, –)	92 (90, 117)	0.373[b]
Post-procedural PA-to-aorta gradient (mmHg), *median (IQR)*	6 (0.5, 10)	2 (0, 10)	0.825[b]
Discharge maximum velocity on stent (m/s), *median (IQR)*	1.75 (1.25, 2.6)	1.5 (1.5, 2)	0.94[b]
Discharge UL/LL oxygen saturation gradient (mmHg), *median (IQR)*	16 (9, 23)	9 (5, 13)	0.26[b]

DAO, Descending Aorta; PA, pulmonary artery. [a]Fisher Exact test; [b]Mann-Whitney *U*-test. Bold values are significant *p*-values.

is particularly seen in non-ductal TPS and presents an additional surgical difficulty during heart-lung transplantation (6, 11). In addition, considering the reduced interventional complexity, and easier post-procedural care of ductal TPS, resuscitation of a tiny or even closed arterial duct is a reasonable good option. Ductal TPS is a safe and effective transcatheter alternative, when applicable, and should be always considered as a life-saving palliation that delays transplantation, especially for young patients with medically refractory PAH. The real question remains whether surgical Potts should be prioritized even over ductal TPS. The better long-lasting outcomes, the no need for reinterventions, and the easier control for transplantation make somehow the surgical Potts a more reasonable option than the TPS

procedure in older children, yet this conclusion deserves further investigation (4, 5, 12).

Previous reports on TPS have commented that patients can often become unstable during the induction of anesthesia (9). Anesthetizing children with severe PAH carries an increased risk of cardiac arrest and death (26, 27). This observation could be considered as an argument against the use of TPS given that the need for multiple reinterventions after this procedure will not only subject small children to increased risk of repeated procedural complications but are also at risk of repeated anesthesia-related perioperative complications.

The shunt size was not addressed in the international Potts registry (12). A direct surgical anastomosis has to be differently assessed than the use of a stent or conduit, both with variable lengths and diameters. In 3D reconstructed views of the LPA and DAO, the tightest DAO-LPA contact area has an elliptic shape stretched along the DAO length and the LPA width (28). The largest diameter of the cross-section's ellipse represents the presumably suitable stent diameter that can be superimposed upon the tightest contact area. To lower supra-systemic PAH to a systemic level, the diameter and length of the Potts shunt should be adjusted according to the DAO diameter that determines the maximal size of the stent that is possible to deploy. Creating a communication of 90% of the DAO diameter can be initially too large, leading to life-threatening hemodynamics. Therefore, we believe that the target diameter of the TPS should be somewhere between 65 and 75% of the DAO diameter. In unstable patients, a 2-step TPS can be an even better option with the initial communication expanded again once the patient has adjusted to the shunt-related pathophysiology.

Is there room for improvement and innovation?

Technically speaking, we believe that ductal-TPS is an already standardized procedure, and the improvement of the technique is somehow limited to the availability of new stent technologies that might implement better material performance, larger functional expansion ranges, flow-reducers, and unidirectional valves as previously evoked for surgical shunts (11, 29). On the other side, the success of the non-ductal TPS is conditioned by both the stability and control of the connection between the fixed DAO and the respiratory-gated movements of the LPA whether during perforation and subsequently throughout the stenting process. The stent bridging technique to create the shunt by reducing the variable space between the 2 vessels turned out somehow inadequate and has been recognized as a bottleneck of the procedure leading to mechanical stent-related complications (e.g., central stent compression, disoriented spatial stent orientation across the vessels, and stent dislodgement) (7). These serious concerns related to the bridged connection have been raised as well for the surgical tube graft and the valved conduit (30). These findings pushed researchers to investigate in experimental models the creation of a connection using magnetic catheters to maintain the required continuous connection and the implantation of a window-like connection device system, spool-shaped self-expanding covered lumen-apposing stents, and most recently the flow regulator devices (18–20). These experimental techniques are promising but none have been tested in humans limiting their actual use. With the leap of faith of researchers and expert interventionists and the continuous advancements in device technology, technical pitfalls can be overcome. Nevertheless, for the present, the resurrection of non-ductal TPS remains conditioned by the availability and efficacy of tailored devices to refine and ease the procedure for widespread acceptance.

Limitations

This is a report from a single yet expert center. The small number of patients remains the main drawback of this study, yet we present the largest single-center experience with TPS.

Conclusion

TPS is a pioneering intervention, especially in the absence of an arterial duct. Procedure survivors have satisfactory long-term survival rates but face both clinical and mechanical stent-related long-term morbidities with frequent need for transcatheter reinterventions. High-pressure post-dilatation of implanted stents during TPS intervention for incomplete stent expansion and/or residual pressure gradient appears to be associated with higher rates of reinterventions during follow-up. In the era of continuous advancements in transcatheter technologies, room for innovation is existent and the challenges have to be properly addressed to meet the better long-term procedural outcomes of surgical Potts shunt.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon request, to any qualified researcher.

Ethics statement

We assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation, and with the Helsinki Declaration of 1975, as revised in 2008. Approval from the Institutional Review Board was obtained (MR004: 2021-1004152008). Informed consent was obtained from participants or their legal guardians/next of kin to use and publish their clinical data before their inclusion in the study.

Author contributions

RH collected all clinical data, performed clinical stratifications, statistical calculations, designed illustrative material, critically analyzed, interpreted the results, and took the lead in writing and revising the entire manuscript. DB, ML, and SM-M supervised the project. All authors discussed the results, read, and approved the final version of the manuscript.

Conflict of interest

Outside the topic of this article, DB received personal fees for advisory committee participation from Novartis, Eli Lilly, Bayer Healthcare, and Janssen-Janssen.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Rachel Hopper,
Stanford University, United States

REVIEWED BY
Allen Everett,
The Johns Hopkins Hospital,
United States
Paul Critser,
Cincinnati Children's Hospital Medical Center, United States

*CORRESPONDENCE
Chantal Lokhorst
c.lokhorst@umcg.nl

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Risk stratification in adult and pediatric pulmonary arterial hypertension: A systematic review

Chantal Lokhorst[1]*, Sjoukje van der Werf[2], Rolf M. F. Berger[1] and Johannes M. Douwes[1]

[1]Department of Pediatric Cardiology, Center for Congenital Heart Diseases, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, [2]Central Medical Library, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

Introduction: Currently, risk stratification is the cornerstone of determining treatment strategy for patients with pulmonary arterial hypertension (PAH). Since the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of pulmonary hypertension recommended risk assessment, the number of studies reporting risk stratification has considerably increased. This systematic review aims to report and compare the variables and prognostic value of the various risk stratification models for outcome prediction in adult and pediatric PAH.

Methods: A systematic search with terms related to PAH, pediatric pulmonary hypertension, and risk stratification was performed through databases PubMed, EMBASE, and Web of Science up to June 8, 2022. Observational studies and clinical trials on risk stratification in adult and pediatric PAH were included, excluding case reports/series, guidelines, and reviews. Risk of bias was assessed using the Prediction model Risk Of Bias Assessment Tool. Data on the variables used in the models and the predictive strength of the models given by c-statistic were extracted from eligible studies.

Results: A total of 74 studies were eligible for inclusion, with this review focusing on model development (n = 21), model validation (n = 13), and model enhancement (n = 9). The variables used most often in current risk stratification models were the non-invasive WHO functional class, 6-minute walk distance and BNP/NT-proBNP, and the invasive mean right atrial pressure, cardiac index and mixed venous oxygen saturation. C-statistics of current risk stratification models range from 0.56 to 0.83 in adults and from 0.69 to 0.78 in children (only two studies available). Risk stratification models focusing solely on echocardiographic parameters or biomarkers have also been reported.

Conclusion: Studies reporting risk stratification in pediatric PAH are scarce. This systematic review provides an overview of current data on risk stratification models and its value for guiding treatment strategies in PAH.

Systematic review registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022316885], identifier [CRD42022316885].

KEYWORDS

pulmonary arterial hypertension, pediatric pulmonary hypertension, risk stratification, risk assessment, survival, outcome, prognosis, children

Introduction

Pulmonary hypertension (PH) is a condition defined by an increased pulmonary arterial pressure. Based on pathophysiological mechanisms, clinical presentation, and hemodynamic characteristics, PH can be classified into five main groups: pulmonary arterial hypertension (PAH, group 1), PH due to left heart disease (group 2), PH due to lung disease and/or hypoxia (group 3), PH due to pulmonary artery obstructions (group 4), and PH with unclear and/or multifactorial mechanisms (group 5) (1). Each PH type can be further divided into multiple subgroups. Group 1 PAH is a progressive and eventually fatal pulmonary vascular disease. Occlusion of small pulmonary arteries leads to increased right ventricular afterload, which eventually results in right ventricular failure.

Initially, the only available treatment option for PAH was calcium channel blockers. However, these calcium channel blockers showed only beneficial to a small subset of patients with a response to acute pulmonary vasodilator testing during right heart catheterization (RHC) (2). Over the last decades, various PAH-targeted therapies have become available, such as endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators, prostacyclin analogues, and selective prostacyclin receptor agonists (3). With the availability of these drugs, the treatment of PAH was initially focused on preventing disease progression and prolonging patient survival. When a patient deteriorated on initial therapy, therapy was escalated to double, triple, or maximal combination therapies. These strategies led to improved patient survival after which the focus of treatment strategies started shifting toward clinical improvement. According to current treatment algorithms, treatment decisions are recommended to be based on the assessment of mortality risk of the individual patient, estimated by using clinical prognosticators, both at initiation of therapy as well as for evaluating treatment response (3–5). Therefore, adequate prediction of risk of mortality is pivotal in the treatment of PAH patients.

To estimate patient risk status, various risk equations and risk stratification models have been established. Initially, risk equations were developed to estimate patient outcome by expressing their chances of survival in a percentage. The first time survival was estimated for PAH patients was in 1991 when D'Alonzo et al. (6) developed the NIH (National Institute of Health registry) risk equation, based on the mean pulmonary arterial pressure (mPAP), mean right atrial pressure (mRAP), and cardiac index (CI). Since then other risk equations have been developed, such as the French PAH registry equation (7), the PHC (Pulmonary Hypertension Connection) survival equation (8), and the REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) risk equation (9). From this original REVEAL risk equation, consisting of nineteen etiologic factors and parameters, the first risk stratification model was derived (10).

Currently, treatment strategies are guided by risk stratification, as proposed by the consecutive European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines for the diagnosis and treatment of PH (3, 4) and the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) expert consensus document on PH (11). According to these strategies, patients are categorized as having low, intermediate, or high risk for mortality, where the aim is to achieve and maintain a low-risk status. The estimated risk is based on multiple clinical, hemodynamic, and echocardiographic parameters with their own cut-off values for each risk category. A risk stratification guided treatment strategy has also been proposed for children with PAH during the World Symposium on Pulmonary Hypertension (WSPH), using the binary strata low and high risk (12, 13).

The aim of this systematic review is to provide an overview of the current risk stratification models in adult and pediatric PAH. With the growing number of risk stratification models it is crucial to assess the reliability and accuracy of these models, especially since their use in daily practice is advocated. Therefore, the two research questions addressed in this systematic review are: (1) which variables are used for risk stratification models in PAH and (2) what is the prognostic value of risk stratification models for transplant-free survival or all-cause mortality?

Methods

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Scoping Reviews (PRISMA) (14). The objectives, inclusion criteria and methods adopted in this systematic review were specified and documented in advance (Prospero registration number: CRD42022316885).

Eligibility criteria

Clinical trials and observational studies focused on risk stratification models both in adult (age $\geq$ 18 years) and pediatric (age $<$ 18 years) PAH patients were eligible for inclusion. Pediatric patients with PH due to lung disease were also considered eligible for inclusion because of the pathological crossover between PAH and the abnormal pulmonary vascular development, seen in developmental lung diseases such as bronchopulmonary dysplasia and congenital diaphragmatic hernia. In these studies the diagnosis had to be confirmed by RHC, or echocardiography in infants with developmental lung disease, and meet the hemodynamic definitions (1). Additionally, the risk stratification model was considered a model only if it comprised at least three variables. Results and conclusions had to be supported by appropriate statistical methods with endpoints defined as transplant-free survival or all-cause mortality. Furthermore, studies had to be written in English.

Studies reporting risk stratification models in adult patients with PH group 2, 3, 4, and 5 according to the Nice 2018 classification (1), and pediatric patients with PH group 2, 4, and 5 were excluded, as well as case reports, case series, guidelines, and reviews. If less than three variables were used for risk stratification models or endpoints other than transplant-free survival or all-cause mortality, studies were excluded as "no risk stratification model" or "not eligible endpoint," respectively. Studies not meeting the inclusion criteria and not fitting any of the above mentioned exclusion reasons were excluded as "other." In this review, survival or risk equations were not considered as risk stratification models.

Information sources and search strategy

Systematic literature searches were conducted in the electronic databases MEDLINE (PubMed), Embase (Elsevier), and Web of Science (Clarivate). The search strategies were developed in collaboration with an information specialist (SW). The structure of the search strategies is based on two concepts: (1) PAH, pediatric PH and (2) risk stratification, risk tooling, prediction modeling. For each concept a search block was developed based on index terms and free text words including synonyms and related terms. No time or language restrictions were applied. The search strategies were initially run at March 3, 2022 and updated at June 8, 2022. The full search strategies can be found in **Supplementary Table 1**.

Managing references and selection process

The results of the database searches were exported to the reference management program EndNote, version 20. In EndNote, duplicate items were determined and removed following the steps described by Bramer et al. (15). The de-duplicated results were exported to the screening program Rayyan.

Two researchers independently performed the screening in Rayyan in two steps. In the title-abstract screening, articles were excluded that were clearly not relevant. Potentially relevant articles and articles with insufficient information in the titles or abstract selected by at least one of the researchers were selected for the full-text screening. In the full-text screening, the two researchers independently judged if the selection criteria were met. Disagreements in decisions between the screeners were solved by a third reviewer. Finally, articles that met the criteria, as agreed by the researchers, were included and divided into four classes judged on the primary aim of the article: (1) model development, (2) model validation, (3) model enhancement, and (4) serial risk stratification. In accordance with the aims of the systematic review, the authors focused on the studies belonging to class 1, 2, and 3. Studies in class 4 focused on risk stratification at follow-up and/or changes in risk score or stratum between baseline and follow-up, whether or not under the influence of intervention, and were hence disregarded from the current review.

Data collection

Data was extracted from the included studies using a standardized data extraction form. Extracted data included: study setting, population demographics and baseline characteristics, variables used in the risk stratification model including cut-off points and defined endpoint, statistical methodology, and the prognostic value of the model.

Analysis

To present an overview of the variables used in risk stratification models, multiple tables were produced. Each table reports the model name or basis, the used definition of risk, the number of risk strata, the number of variables, and specifies

which variables are used for the model. Separate tables were created for the renowned risk stratification models (containing both development and validation), the lesser studied models, model enhancement, and pediatric risk stratification strategies.

For the evaluation of the prognostic value of the risk stratification models, the reported c-statistic was used. The c-statistic is equivalent to the area under the receiver operating characteristic curve (AUROC) and is a measure of the discriminatory ability. It can be interpreted as the probability that a patient who died had a higher predicted probability of death than a patient who survived. A c-statistic of 1.0 shows a perfect prediction, whereas a c-statistic of 0.5 is indicative of poor prediction and the model is no better than chance. Hence, the model with the higher c-statistic (or greater AUROC) is better at discriminating between survival and death (17).

Risk of bias

Risk of bias (ROB) was assessed using the Prediction model Risk Of Bias Assessment Tool (PROBAST) for every study and in case of studies including multiple models, separately for the different risk stratification models (16). This tool consists of four domains - participants, predictors, outcome, and analysis–with a total of 20 signaling questions to assist in assessing ROB. These questions can be answered as (probably) yes, (probably) no, or no information, with "no" indicating potential bias. For model development studies, the development signaling questions were answered, and for validation studies the validation questions. In the case of studies reporting both the development of a model and the validation of this model or other models, both the development and validation signaling questions were answered for each model separately. For model enhancement studies, the development questions were acknowledged, as well as the validation questions when the original model was also validated. Besides ROB, the applicability of the model was evaluated to determine the relevance of the participants, predictors, and outcome to the research question. ROB and applicability assessment was performed by one researcher, but when in doubt, a second researcher was consulted.

Results

Identified studies

In **Figure 1**, the PRISMA flowchart for the identification of studies is shown. A total of 2,395 records were identified from the databases. After duplicate removal, 1,539 studies remained for abstract screening of which 1,385 were excluded during abstract screening. Of the 154 full-text screened studies, 80 were excluded (**Supplementary Table 2**). The remaining 74 studies were considered eligible for inclusion (**Supplementary Table 3**), of which two studies involved pediatric PAH patients. No studies concerning risk stratification in pediatric PH due to lung disease were retrieved, as such our results focus on RHC confirmed PAH only. The 31 studies concerning serial risk stratification were disregarded, since the current study focusses solely on model development (n = 21), validation (n = 13), and enhancement (n = 9) of risk stratification models, resulting in a total of 43 studies to be discussed in this review. The main characteristics of these 43 studies are presented in **Tables 1–3** for respective development, validation, and enhancement studies.

Variables in risk stratification

We have identified multiple risk stratification models, such as the REVEAL risk calculator and the ESC/ERS 2015 guidelines-based COMPERA, SPARH, FPRH invasive and non-invasive models, and other abbreviated versions of the ESC/ERS 2015 guidelines. In **Table 4** an overview of the variables used for these risk stratification models is given, along with the total number of variables used in each model, the risk definition, and the number of strata.

The first REVEAL risk calculator was developed by Benza et al. (10) in 2012 and consisted of twelve variables: WHO Functional Class (WHO-FC), 6-minute walk distance (6MWD), N-terminal-pro brain natriuretic peptide (NT-proBNP, or brain natriuretic peptide–BNP), pericardial effusion, mRAP, pulmonary vascular resistance (PVR), WHO group 1 subgroup, male older than 60 years of age, renal insufficiency, systolic blood pressure (SBP), heart rate (HR), and percentage predicted carbon monoxide lung diffusing capacity (DL_{CO}). Points are assigned to every variable, with its weight based on the results of the multivariable Cox proportional hazard model. In 2019, Benza et al. (18) updated some of the cut-off values of the variables and added an extra variable to the model, all-cause hospitalizations within the last 6 months, resulting in the REVEAL 2.0 calculator. The REVEAL Lite 2, a non-invasive, abbreviated version of the REVEAL 2.0 calculator, was published by Benza et al. (19) in 2021.

Many different methods have been developed based on the risk stratification as recommended by the ESC/ERS 2015 guidelines. In 2017, Hoeper et al. (20) reported the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) model which uses six variables: WHO-FC, 6MWD, NT-proBNP (or BNP), mRAP, CI, and mixed venous oxygen saturation (SvO_2). Each variable is assigned a grade 1 (low risk), 2 (intermediate risk), or 3 (high risk) according to the cut-off values derived from the ESC/ERS 2015 guidelines. To determine the risk class, the sum of these grades is divided by the number of available variables and rounded to the nearest integer. Kylhammar et al. (21) created a similar method with SPAHR (Swedish PAH Register), but included two more variables: right atrial (RA) area and pericardial effusion. Since many patients were stratified as having intermediate risk, Hoeper et al. (22) created the

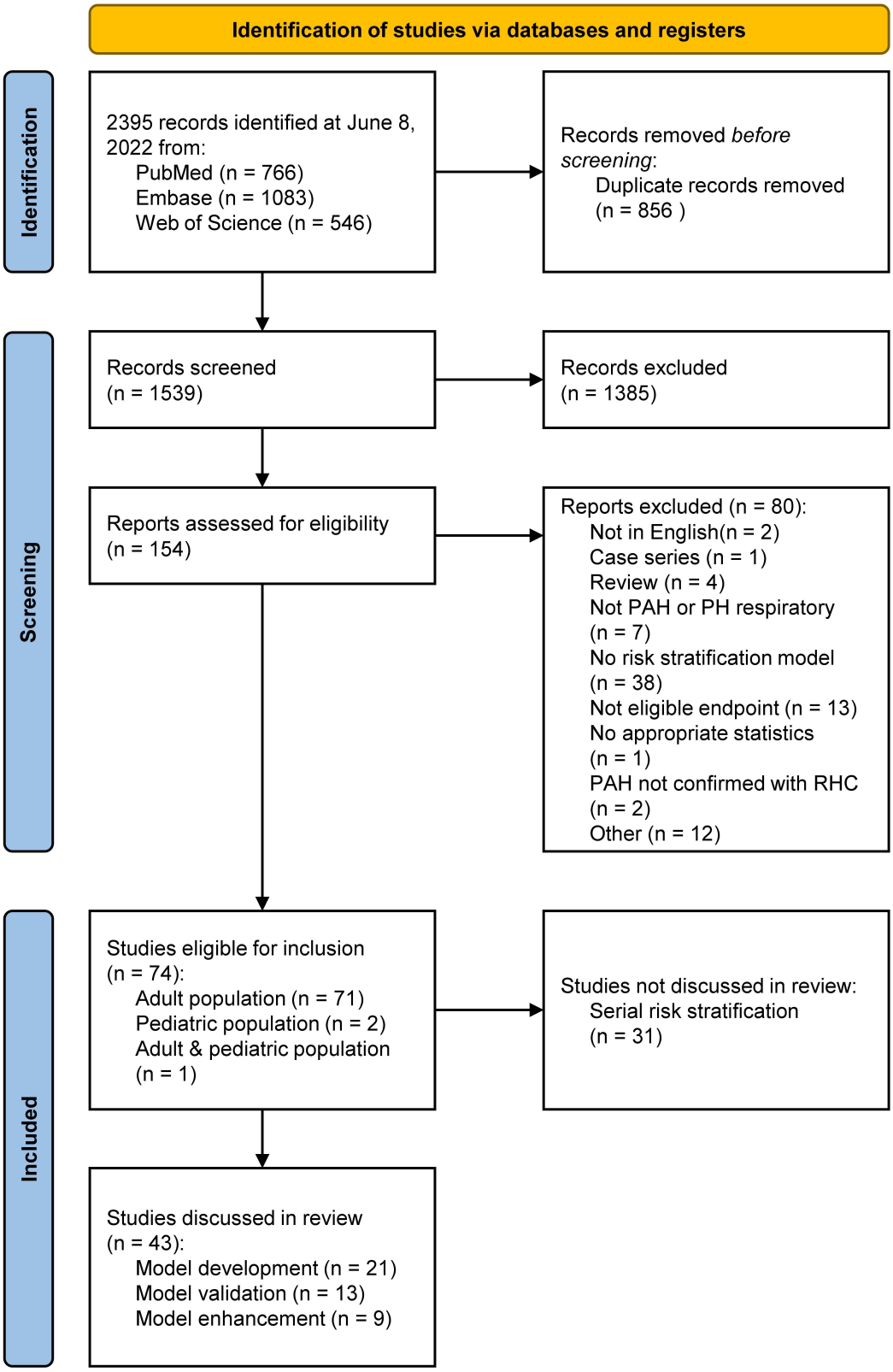

FIGURE 1
PRISMA flowchart showing the study selection. PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RHC, right heart catheterization. Other reasons included editorials, retracted articles, and commentaries.

TABLE 1 Study characteristics of studies describing model development.

Study	Cohort	Study site	Study baseline	Endpoint	C-statistic	Patients *n*	Age (years)	Female%	IPAH/HPAH%	PAH-CHD%	PAH-CTD%	PAH other%	WHO-FC	6MWD (m)	NT-proBNP (pg/ml)	mRAP (mmHg)	mPAP (mmHg)	CI (L/min/m^2)	PVR (WU)
Austin (37)	Der	USA Florida	E	TFS	1 year	175	60	69	43	5	35	17	2.7	299	358ˆ	8.7	45	2.4	8.3*
	Val	USA Rochester	E	TFS	1 year	677	53.7	75	48	11	28	13		327			52	2.5	
Benza (10)	Der	USA multicenter	E	ACM	1 year	2716	50.4	78.6	49.4	11.8	23.9	15	2.5	370	1455	8.6	49.5	2.6	10.5*
	Val	USA multicenter	D	ACM	1 year	504	53	74	50	4.8	31	14.3	2.9	308	2705	10.0	48.8		10.7
Benza (18)		USA multicenter	1 year post E	ACM	1 year	2529	53.6	80	48.2	9.6	25.7	16.5	2.5	374	1730	8.7	48.5		9.6
Benza (19)		USA multicenter	1 year post E	ACM	1 year	2529	53.6	80	48.2	9.6	25.7	16.5	2.5	374	1730	8.7	48.5		9.6
Boucly (23)		Canada Ottawa	D	TFS	5 year	211	63.2	64.6	69.8	6.6	23.7		2.8	272	3152	7.9	44.9	2.17	9.8
Chiu (24)		Taiwan multicenter	E	ACM		87	37.4	31		100			2.4	385	1748	6.5	56.7	2.4	11.2
Dardi (25)		Italy Bologna	D	ACM	1 year	725	51*	69	55.9	20.2	23.9		2.9	389*	807*	7*	53*	2.4*	11*
Ghio (38)		EU and USA multicenter	E	ACM		517	52	61.1	64.8	8.4	14.1	12.7	2.8	358					
Haarman (45)		Netherlands Groningen	D	TFS	5 year	58	6.8*	53.4	100				2.8						
Haddad (41)		USA Stanford	E	TFS	5 year	231	48*	78.8			32		2.6	430*	407*	7.0*	50.1	2.0*	
Hoeper (20)		EU multicenter	D	ACM		1588	64	64	67	4	22	7	3.0	298	1573*	8	45	2.3	9.8
Hoeper (22)		EU multicenter	D	ACM		1655	65.7	64.3	71.4	2.8	19.9	5.8	3.0	293	1499*	8.2	43.3	2.2	9.3
Imai (26)		Japan Nagoya	E	ACM		80	48	79	36	13	36	15	2.5	370	75*ˆ	5.9	45	2.9	8.9
Kylhammar (21)		Sweden multicenter	D	ACM		530	68**	64.7	50.6	12.6	30.6	6.2							
Lee (52)	Der	UK Glasgow	D	ACM		182	62*	69	54		32	13	2.9	260*	1026*	7*	47*		10.8*
	Val	UK Cambridge	D	ACM		99	53*	27	100				2.9	267*	2029*	9*	50*		13.3*
Li (27)		China Nanjing	D	ACM		50	39.1	94			100		2.8	370	1790	7	45.6	2.7	10.6
Mercurio (28)		USA Baltimore	D	ACM		151	61	84.8			100††								
Rhodes (39)	Der**	UK multicenter	E	TFS	5 year	238	39.1*	74	100				2.9	353*		9*	55*	2.0*	12.6*
	Val	France multicenter	D	TFS	5 year	79	41.9*		84.8			15.2	2.6	360*		8*	50*	2.39*	9.9*
Wang (29)		China multicenter	D	ACM		103	43.2	98			100†		2.3	398	822*	6.4	48.1	2.6	11.5
Xiong (31)	Der	China Shanghai	E	ACM	1 year	108	52.8	71.3	47.2	9.3	32.4	11.1	2.7	338	3268	9.7	45.2		10.5
	Val	China Shanghai	E	ACM	1 year	216	54.6	73.6	49.1	11.6	28.7	14.6	2.7	309	3497	10.6	46.7		11.2
Yogeswaran (40)	Der	Germany Giessen	D	ACM		227	49*	67	100				3.0	335	265ˆ		50.5	2.1	11.2*
	Val	Germany Hamburg	D	ACM		234	67*	64						309	2960		44.0	2.3	7.8*

Values reported as mean, unless stated otherwise. PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, hereditary PAH; CHD, congenital heart disease; CTD, connective tissue disease; WHO-FC, WHO functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; Der, derivation; Val, validation; D, diagnosis; E, enrollment; TFS, transplant-free survival; ACM, all-cause mortality. *Median, **subgroup, $indexed PVRI, ˆBNP, †primary Sjögren's syndrome, and ††systemic sclerosis.

abbreviated version COMPERA 2.0 model in 2021, where the intermediate risk stratum is split into intermediate-low and intermediate-high risk, resulting in a four-strata model consisting of three variables: WHO-FC, 6MWD, and NT-proBNP. The FPHR (French pulmonary hypertension registry) invasive and non-invasive method, published by Boucly et al. (23) in 2017, uses the number of low-risk criteria to estimate the mortality risk. WHO-FC, 6MWD, mRAP, and CI are used in the invasive method, whereas WHO-FC, 6MWD, and NT-proBNP (or BNP) are used in the non-invasive method. A major limitation of this method is that it cannot be applied if one of the variables is missing. Besides COMPERA, SPAHR, and FPHR models, other abbreviated versions of the ESC/ERS 2015 guidelines were reported (24–33). The variables used in these models are also shown in **Table 4**. From this table it can be observed that most often used variables in risk stratification models are WHO-FC, 6MWD, NT-proBNP, mRAP, CI, and SvO_2.

The enhancement of above mentioned risk stratification models has been explored by several studies by adding one or more imaging or biomarker variables to the models, such as the right ventricular end-systolic volume index (34), estimated

TABLE 2 Study characteristics of studies describing model validation.

Study	Cohort	Study site	Study baseline	Endpoint	C-statistic	Patients *n*	Age (years)	Female%	IPAH/HPAH%	PAH-CHD%	PAH-CTD%	PAH other%	WHO-FC	6MWD (m)	NT-proBNP (pg/ml)	mRAP (mmHg)	mPAP (mmHg)	CI (L/min/m^2)	PVR (WU)
Anderson (53)		Australia and New Zealand multicenter	1 year post E	ACM	1 year	1011	58.2	77.1	49	9.9	31.0	10.1	2.6	383.7		8.5			7.5
Boucly (42)		France multicenter	D	ACM	1 year	2879	61	60	43	1	27	29	2.7	300*	995*	8	45	2.6	8.8
Chang (54)		USA multicenter	E	ACM		935	56*	76	43	5	32	14	2.6	335	603*	10	49.5	2.3	9.1*
Gong (55)		China Shanghai	D	ACM		392	40	67	100				2.6	379	748*	6*	58*	2.4*	14*
Hjalmarsson (56)		Sweden multicenter	D	TFS		502	68*	65	61		39		2.9	267*	1573*	7*	45*	2.3*	9*
Kylhammar (57)		Sweden multicenter	D	TFS		252	53*	73	46	13	33	8	2.8	373*	803*	6*	47*	2.5*	8.7*
Mullin (58)	JHPHP	USA Baltimore	D	ACM	1 year	117	62.3	81.2			100††		2.6	319*	942*	8	40	2.5	8.1
	PHAROS	USA and Canada multicenter	E	ACM	1 year	175	60	88.9			100††		2.4	366*	331.5*		37		6.5
Qu (59)		China multicenter	D	ACM	1 year	306	35	99.3			100¥		2.5	409	1848	5.9	46.9		11.0
Quan (46)		China multicenter	D	ACM	1 year	2031	35	76.2	38.8	45.2	13.1	3.0	2.2	412	1393	6.5	59.8	3.1	13.7
Sitbon (60)		France multicenter	E	ACM	1 year	1737	54.7	58.8	41.2	8.7	21.5	28.6	2.7	356		7.7	48.3	2.6	9.7
Vraka (61)		Switzerland Lausanne	D	TFS	3 year	50	54.8	68	56	8	14	22	2.8	326	1847	8.6	47.4	2.6	9.6
Weatherald (48)		France multicenter	D	TFS	1 year	513	67.8*	78.3			100		2.8	285*	1144*	6*	40*	2.5*	7.5*
Xanthouli (30)		Germany Heidelberg	D	ACM		142	63.3	61.3	33.8		26.1		2.9	333	2334	7.9	43.2	2.4	8.1

Values reported as mean, unless stated otherwise. PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, hereditary PAH; CHD, congenital heart disease; CTD, connective tissue disease; WHO-FC, WHO functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; D, diagnosis; E, enrollment; TFS, transplant-free survival; ACM, all-cause mortality; JHPHP, Johns Hopkins Pulmonary Hypertension Program; PHAROS, Pulmonary Hypertension Assessment and Recognition of Outcome in Scleroderma Registries. *Median, †† systemic sclerosis, and ¥ systemic lupus erythematosus.

glomerular filtration rate (eGFR) (33), or endostatin (35). To enhance the performance of the REVEAL 2.0 calculator, Kanwar et al. (36) produced a tree-augmented naïve Bayes version using the same variables and cut-off values as the REVEAL 2.0 calculator. In **Table 5** an overview of the model enhancement studies with the variables is presented.

Additionally, others have tried to create risk stratification models based solely on echocardiographic parameters (37, 38) or biomarkers (39, 40) (**Table 6**). For example, Ghio et al. (38) used the echocardiographic parameters tricuspid annular plane systolic excursion (TAPSE), degree of tricuspid regurgitation (TR) and a marker of systemic venous congestion represented by inferior vena cava diameter. Yogeswaran et al. (40) developed a model with the biomarkers γ-glutamyl transferase (GGT), aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, and neutrophil-to-lymphocyte ratio (NLR). A different approach for developing a risk stratification model was shown by Haddad et al. (41). They attempted to model the data architecture by creating a network graph. This graph shows the connectivity of every parameter with the other parameters and identified NT-proBNP as the most central (important) parameter.

Prognostic value of risk stratification models

The prognostic value of the REVEAL risk scores in different studies and populations is shown in **Figure 2** by a forest plot of the c-statistic with its 95% confidence interval (95% CI). The c-statistic was found to range from 0.70 to 0.75 for the REVEAL risk score calculator and from 0.65 to 0.74 for the REVEAL 2.0 calculator. REVEAL Lite 2 had a c-statistic of 0.70.

In **Figure 3**, the c-statistics of the risk stratification models based on the ESC/ERS 2015 guidelines are presented. C-statistic ranged from 0.62 to 0.77 for the COMPERA model, and from 0.56 to 0.73 and 0.39 to 0.69 for the FPHR invasive and non-invasive method, respectively. The COMPERA 2.0 model showed a c-statistic of 0.67 in a validation study by Boucly et al. (42). Other abbreviated versions of the ESC/ERS 2015 guidelines c-statistic ranged from 0.60 to 0.73. Highest c-statistic was reported by Xiong et al. (31) with a model consisting of the non-invasive variables WHO-FC, 6MWD, NT-proBNP, and RA area.

Several enhancement studies were found to have an increase in c-statistic upon the addition of an imaging or serum

TABLE 3 Study characteristics of studies describing model enhancement.

Study	Cohort	Study site	Study baseline	Endpoint	C-statistic	Patients *n*	Age (years)	Female%	IPAH/HPAH%	PAH-CHD%	PAH-CTD%	PAH other%	WHO-FC	6MWD (m)	NT-proBNP (pg/ml)	mRAP (mmHg)	mPAP (mmHg)	CI (L/min/m^2)	PVR (WU)
Griffiths (44)		USA multicenter	E	ACM		182	13*	59	52.2	37.9	3.3	6.6	2.4	423*	218*	7*	54*	3.7*	10.7*$
Harbaum (43)		Germany multicenter	D	TFS		204	56	67	96			4	2.8	340	2932	9	59	2.2	12
Kanwar (36)	Internal validation REVEAL 2.0	USA multicenter	E	ACM	1 year		53.6	80.0	49.2		25.7	13.4	2.5						
	External validation COMPERA	EU multicenter	D	ACM	1 year			64.3	48.3		35.0	7	2.9						
	External validation PHSANZ	Australia and New Zealand multicenter	E	ACM	1 year			77.7	49.9		32.2	17.4	2.6						
Lewis (34)		UK multicenter	D	ACM	1 year	438	56.6	75	45	9	37	9	2.8			10	48	2.8	8.9
Lewis (62)		UK multicenter	D	TFS	1 year	1240	64*	71	48.6		51.4		3.1			9*	48*	2.4*	9.1*
Simpson (35)		USA multicenter	E	ACM		2017	55	80	43.1		30.9	26	2.6	347	672*	9	50	2.7	10
Vicenzi (63)		Belgium Brussels	D	TFS		102	54	62.7	57.8	13.7	14.7	13.8	3.0	415*	1077*				
Yogeswaran (32)		Germany Giessen	D	ACM		301	58	65								6.3	45		8.9
Zelt (33)		Canada Ottowa	D	TFS	5 year	211	63.2	64.6	69.8	6.6	23.7		2.8	272	3152	7.9	44.9	2.17	9.8

Values reported as mean, unless stated otherwise. PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, hereditary PAH; CHD, congenital heart disease; CTD, connective tissue disease; WHO-FC, WHO functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; CI, cardiac index; PVR, pulmonary vascular resistance: D, diagnosis; E, enrollment; TFS, transplant-free survival; ACM, all-cause mortality. *Median and $PVRI.

biomarker to a previously described model (**Figure 4**). Lewis et al. reported an increase in c-statistic of the REVEAL 2.0 calculator from 0.74 (0.65–0.83) to 0.78 (0.70–0.87) upon addition of the right ventricular end-systolic volume index. Harbaum et al. (43) increased the c-statistic of the COMPERA model from 0.62 (0.52–0.73) to 0.67 (0.57–0.79) by adding arterial carbon dioxide partial pressure to the model. Addition of biomarkers NT-proBNP and endostatin to the FPHR invasive method was shown to increase the c-statistic from 0.62 to 0.72 (35), and endostatin also increased the c-statistic of the FPHR non-invasive method from 0.68 to 0.71 (35).

The c-statistics of other developed risk stratification models are presented in **Figure 5**. A model using the plasma proteome had c-statistics of 0.82 (0.77–0.88) and 0.74 (0.63–0.85) in the derivation and validation cohort, respectively (39). The eigenvector centrality model developed by Haddad et al. (41) had a c-statistic of 0.81 (0.77–0.85).

Risk stratification in pediatric pulmonary arterial hypertension

Only two studies reporting risk stratification in pediatric PAH were found eligible for inclusion. Griffiths et al. (44) applied the REVEAL 2.0 calculator in 182 children with a median age (interquartile range–IQR) of 13 (8–17) years. They used the variables and cut-off values from the REVEAL 2.0 calculator, except for renal insufficiency, and categorized the patients according to the five risk strata from the original REVEAL risk score calculator (**Table 7**). The reported c-statistic (**Figure 6**) of the model in this pediatric population was 0.69 (0.56–0.83). Addition of soluble suppressor of tumorigenicity-2 increased the c-statistic to 0.78 (0.65–0.89). The other pediatric PAH study was by Haarman et al. (45) and described the development of two risk stratification models in 58 children with a median age of 6.8 (2.2–13.4) years. The models were based on the variables and cut-off values recommended by the WSPH 2013 pediatric task force (12) with the addition of two variables from the ESC/ERS 2015 guideline (3) and risk was defined as the number of low risk criteria. The first model consisted of the following variables: WHO-FC, NT-proBNP, mRAP, CI, TAPSE, syncope, height, body mass index, mPAP/mean systemic arterial pressure ratio, indexed PVR, acute vasoreactivity, SvO_2, and RA area. The second model contained only the non-invasive variables of the first model (**Table 7**). C-statistic of the full model was 0.78 (0.64–0.92), and remained almost similar in the non-invasive version to 0.76 (0.62–0.90) (**Figure 6**).

TABLE 4 Variables used in REVEAL and ESC/ERS 2015 guideline-based risk stratification models: development and validation studies.

Study	Model name	Definition of risk	Strata	Number of variables	WHO-FC	6MWD	NT-proBNP	BNP	Peak VO_2	RA area	Pericardial effusion	mRAP	CI	SvO_2	PVR	WHO group 1 subgroup	Male age > 60	Renal insufficiency	eGFR	Systolic BP	Heart Rate	% predicted DL_{CO}	All-cause hospitalizations ≤ 6 months	Syncope	Clinical signs RHF
Benza (10), Austin (37), Mullin (58), Qu (59), Sitbon (60), Xiong (31), Zelt (33)	REVEAL risk score calculator	Risk category based on total score	5	12																					
Benza (18), Anderson (53), Harbaum (43), Lewis (34), Quan (46), Simpson (35), Vraka (61), Zelt (33)	REVEAL 2.0 calculator	Risk category based on total score	3	13			OR	OR										OR	OR						
Benza (19), Chang (54), Quan (46)	REVEAL Lite 2	Risk category based on total score	3	6			OR	OR										OR	OR						
Hoeper (20), Benza (18), Chang (54), Dardi (25), Gong (55), Harbaum (43), Quan (46), Vicenzi (63), Vraka (61), Xanthouli (30), Yogeswaran (40)	COMPERA model	Risk category based on average score	3	6			OR	OR																	
Hoeper (22), Boucly (42)	COMPERA model (abbreviated)	Risk category based on average score	3	3			OR	OR																	
Hoeper (22), Boucly (42)	COMPERA 2.0 model	Risk category based on average score	4	3			OR	OR																	

(Continued)

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TABLE 4 (Continued)

Study	Model name	Definition of risk	Strata	Number of variables	WHO-FC	6MWD	NT-proBNP	BNP	Peak VO_2	RA area	Pericardial effusion	mRAP	CI	SvO_2	PVR	WHO group 1 subgroup	Male age > 60	Renal insufficiency	eGFR	Systolic BP	Heart Rate	% predicted DL_{CO}	All-cause hospitalizations ≤ 6 months	Syncope	Clinical signs RHF
Kylhammar (21), Hjalmarsson (56), Kylhammar (57)	SPAHR model	Risk category based on average score	3	8	■	■	■			■	■	■	■	■											
Boucly (23), Benza (18), Chang (54), Dardi (25), Mercurio (28), Quan (46), Simpson (35), Vicenzi (63), Vraka (61), Weatherald (48), Zelt (33)	FPHR invasive model	#low risk criteria	3	4	■	■						■	■												
Boucly (23), Harbaum (43), Quan (46), Simpson (35), Vicenzi (63), Xanthouli (30)	FPHR non-invasive model	#low risk criteria	3	3	■	■	OR	OR																	
Chiu (24)	ESC/ERS 2015 (abbreviated, non-invasive)	#high risk criteria	2	3	■	■	OR	OR																	
Dardi (25)	ESC/ERS 2015 (abbreviated)	Other	3	6	■	■	OR	OR				■	■	■											
Imai (26)	ESC/ERS 2015 (abbreviated)	Risk category based on average score	3	7	■	■		■	■			■	■	■											
Li (27)	ESC/ERS 2015 (abbreviated)	Other	3	7	■	■	■				■	■	■	■											

(Continued)

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TABLE 4 (Continued)

Study	Model name	Definition of risk	Strata	Number of variables	WHO-FC	6MWD	NT-proBNP	BNP	Peak VO_2	RA area	Pericardial effusion	mRAP	CI	SvO_2	PVR	WHO group 1 subgroup	Male age > 60	Renal insufficiency	eGFR	Systolic BP	Heart Rate	% predicted DL_{CO}	All-cause hospitalizations ≤ 6 months	Syncope	Clinical signs RHF
Mercurio (28)	ESC/ERS 2015 (abbreviated)	Risk category based on average score	3	5																					
Wang (29)	ESC/ERS 2015 (abbreviated)	Other	3	6			OR	OR																	
Xanthouli (30)	ESC/ERS 2015 (abbreviated, non-invasive)	Risk category based on average score	3	4																					
Xiong (31)	ESC/ERS 2015 (abbreviated, non-invasive)	Risk category based on total score	3	4																					
Yogeswaran (32)	ESC/ERS 2015 (abbreviated)	Risk category based on average score	3	5																					
Zelt (33)	ESC/ERS 2015 (abbreviated)	Risk category based on average score	3	10																					

WHO-FC, WHO functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; BNP, brain natriuretic peptide; peak VO_2, peak oxygen consumption; RA area, right atrial area; mRAP, mean right atrial pressure; CI, cardiac index; SvO_2, mixed venous oxygen saturation; PVR, pulmonary vascular resistance; eGFR, estimated glomerular filtration rate; BP, blood pressure; DL_{CO}, carbon monoxide lung diffusing capacity; RHF, right heart failure.

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TABLE 5 Variables used in REVEAL and ESC/ERS 2015 guideline-based risk stratification models: enhancement studies.

Study	Model name	Definition of risk	Strata	Number of variables	WHO-FC	6MWD	NT-proBNP	BNP	Pericardial effusion	mRAP	CI	SvO_2	PVR	WHO group 1 subgroup	Male age > 60	Renal insufficiency	eGFR	Systolic BP	Heart Rate	% predicted DL_{CO}	All-cause hospitalizations ≤1	Syncope	Clinical signs RHF	TAPSE/sPAP	$PaCO_2$	ISWD	RVESVi	TAPSE/TRV	Endostatin
Zelt (33)	REVEAL risk score calculator + eGFR	Risk category based on total score	3	12												OR	OR												
Harbaum (43)	REVEAL 2.0 calculator + $PaCO_2$	Risk category based on total score	3	14			OR	OR								OR	OR												
Lewis (34)	REVEAL 2.0 calculator + RVESVi	Risk category based on total score	3	14			OR	OR								OR	OR												
Lewis (62)	REVEAL 2.0 calculator ISWD	Risk category based on total score	3	13			OR	OR								OR	OR												
Simpson (35)	REVEAL 2.0 calculator + endostatin	Risk category based on total score	3	14			OR	OR								OR	OR												
Kanwar (36)	REVEAL 2.0 tree-augmented naïve Bayes	Other	3	13			OR	OR								OR	OR												
Harbaum (43)	COMPERA model + $PaCO_2$	Risk category based on average score	3	7			OR	OR																					
Vicenzi (63)	COMPERA model + TAPSE/TRV or TAPSE/sPAP	Risk category based on average score	4	7			OR	OR																OR				OR	
Lewis (34), Lewis (62)	FPHR invasive model ISWD	#low risk criteria	3	4																									
Lewis (34)	FPHR invasive model ISWD + RVESVi	#low risk criteria	3	5																									

(Continued)

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TABLE 5 (Continued)

Study	Model name	Definition of risk	Strata	Number of variables	WHO-FC	6MWD	NT-proBNP	BNP	Pericardial effusion	mRAP	CI	SvO_2	PVR	WHO group 1 subgroup	Male age > 60	Renal insufficiency	eGFR	Systolic BP	Heart Rate	% predicted DL_{CO}	All-cause hospitalizations ≤ 6 months	Syncope	Clinical signs RHF	TAPSE/sPAP	$PaCO_2$	ISWD	RVESVi	TAPSE/TRV	Endostatin
Simpson (35)	FPHR invasive model + NTproBNP	#low risk criteria	3	5																									
Simpson (35)	FPHR invasive model + endostatin	#low risk criteria	3	5																									
Simpson (35)	FPHR invasive model + NTproBNP + endostatin	#low risk criteria	3	6																									
Vicenzi (63)	FPHR invasive model + TAPSE/TRV or TAPSE/sPAP	#low risk criteria	4	5																				OR				OR	
Zelt (33)	FPHR invasive model + eGFR	#low risk criteria	3	5																									
Harbaum (43)	FPHR non-invasive model + $PaCO_2$	#low risk criteria	3	4			OR	OR																					
Simpson (35)	FPHR non-invasive model + endostatin	#low risk criteria	3	4			OR	OR																					
Vicenzi (63)	FPHR non-invasive model + TAPSE/TRV or TAPSE/sPAP	#low risk criteria	4	4			OR	OR																OR				OR	
Yogeswaran (32)	ESC/ERS 2015 (abbreviated) + TAPSE/sPAP	Other	4	6																									
Zelt (33)	ESC/ERS 2015 (abbreviated) + eGFR	Risk category based on average score	3	11																									

WHO-FC, WHO functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; BNP, brain natriuretic peptide; mRAP, mean right atrial pressure; CI, cardiac index; SvO_2, mixed venous oxygen saturation; PVR, pulmonary vascular resistance; eGFR, estimated glomerular filtration rate; BP, blood pressure; DL_{CO}, carbon monoxide lung diffusing capacity; RHF, right heart failure; TAPSE/sPAP, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio; $PaCO_2$, arterial carbon dioxide partial pressure; ISWD, incremental shuttle walk distance; RVESVi, right ventricular end-systolic volume index; TAPSE/TRV, tricuspid annular plane systolic excursion/tricuspid regurgitation velocity ratio.

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TABLE 6 Variables used in other risk stratification models.

Study	Model name	Definition of risk	Strata	Number of variables	6MWD	NT-proBNP	Pericardial effusion	mRAP	TAPSE	WHO group 1 subgroup	Systolic BP	Heart Rate	% predicted DL_{CO}	Age	Sex	CO	CTD etiology	TR	dilated IVC	eRAP	RVESRI	Sodium	Albumin	GGT	AST/ALT	NLR	SVEP1	PXDN	Renin	NRP1	TSP2	PRDX4
Austin (37)	Echocardiographic approach	# high risk criteria	2	3			■											■		■												
Ghio (38)	Echocardiographic approach	low risk: TAPSE > 17 mm and TR grade 0–1; intermediate risk: TAPSE > 17 mm and TR 2–3 OR TAPSE ≤ 17 mm and normal IVC; high risk: TAPSE ≤ 17 mm and dilated IVC	3	3					■									■	■												
Haddad (41)	Eigenvector centrality model	based on the normally distributed prognostic index (weighted sum of coefficients)	5	9	■	■			■		■		■		■		■				■	■	■								
Haddad (41)	Eigenvector centrality model–biomarker-focused	based on the normally distributed prognostic index (weighted sum of coefficients)	5	7	■	■					■	■										■									
Haddad (41)	Eigenvector centrality model – imaging-focused	Based on the normally distributed prognostic index (weighted sum of coefficients)	5	8	■						■	■					■			■	■		■								
Lee (52)	Scottish composite score	Risk category based on total score	3	6	■			■		■				■	■	■															
Rhodes (39)	Plasma proteome 6 + NT-proBNP	Risk category based on total score	2	7		■																					■	■	■	■	■	■
Rhodes (39)	Plasma proteome 6	Risk category based on total score	2	6																												
Yogeswaran (40)	Biomarker approach	Risk category based on average score	3	3																					■	■	■					

6MWD, 6-minute walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; mRAP, mean right atrial pressure; TAPSE, tricuspid annular plane systolic excursion; BP, blood pressure; DL_{CO}, carbon monoxide lung diffusing capacity; CO, cardiac output; CTD, connective tissue disease; TR, tricuspid regurgitation; IVC, inferior vena cava; eRAP, estimated right atrial pressure; RVESRI, right ventricular end-systolic volume index; GGT, γ-glutamyl transferase; AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio; NLR, neutrophil-to-lymphocyte ratio.

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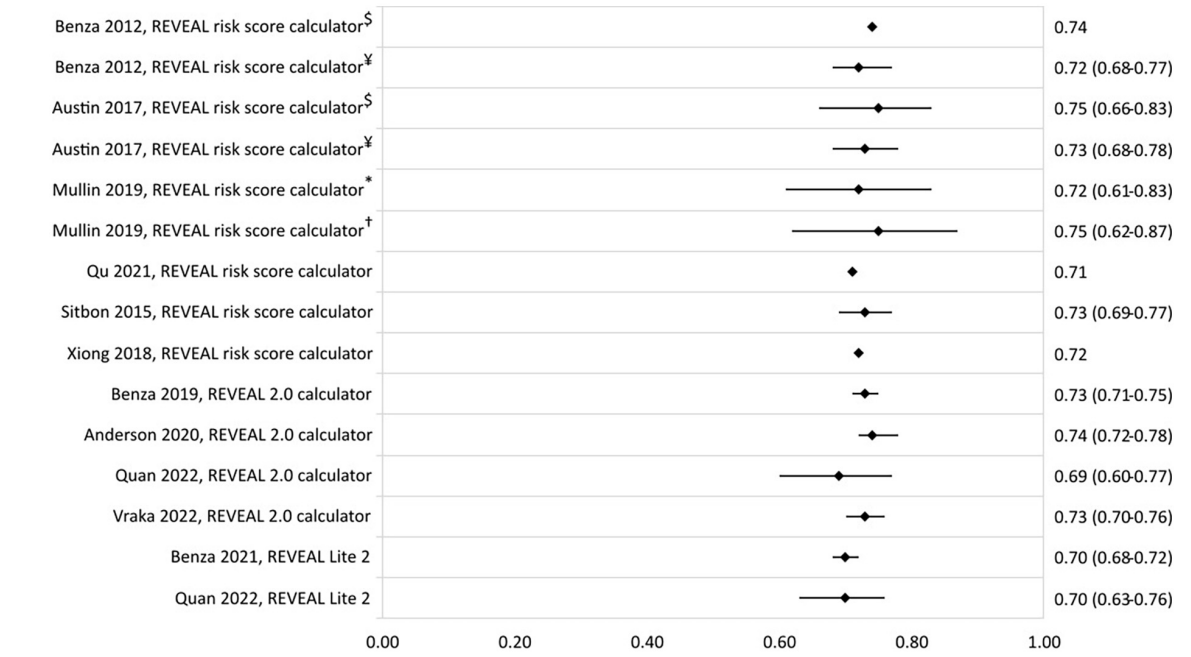

FIGURE 2
C-statistic (95% CI) of the development and validation of REVEAL risk stratification models. $Derivation cohort, ¥validation cohort, *JHPHP, and †PHAROS.

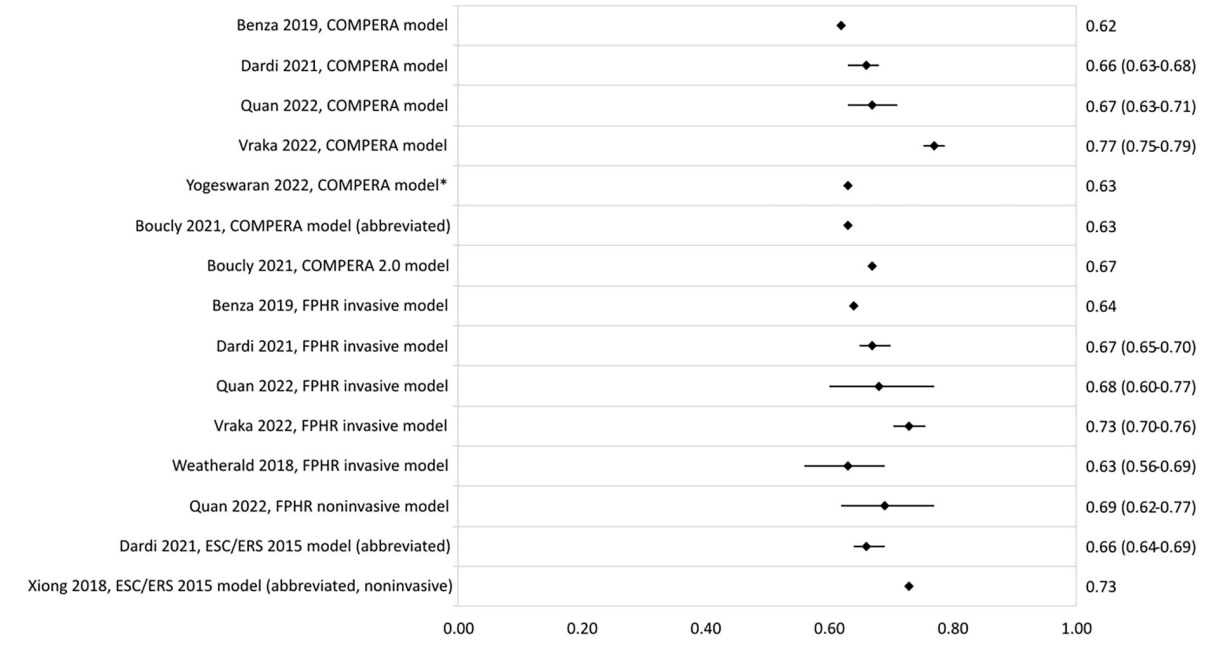

FIGURE 3
C-statistic (95% CI) of the development and validation of ESC/ERS 2015 guideline-based models. *Cohort includes PAH and chronic thromboembolic PH patients.

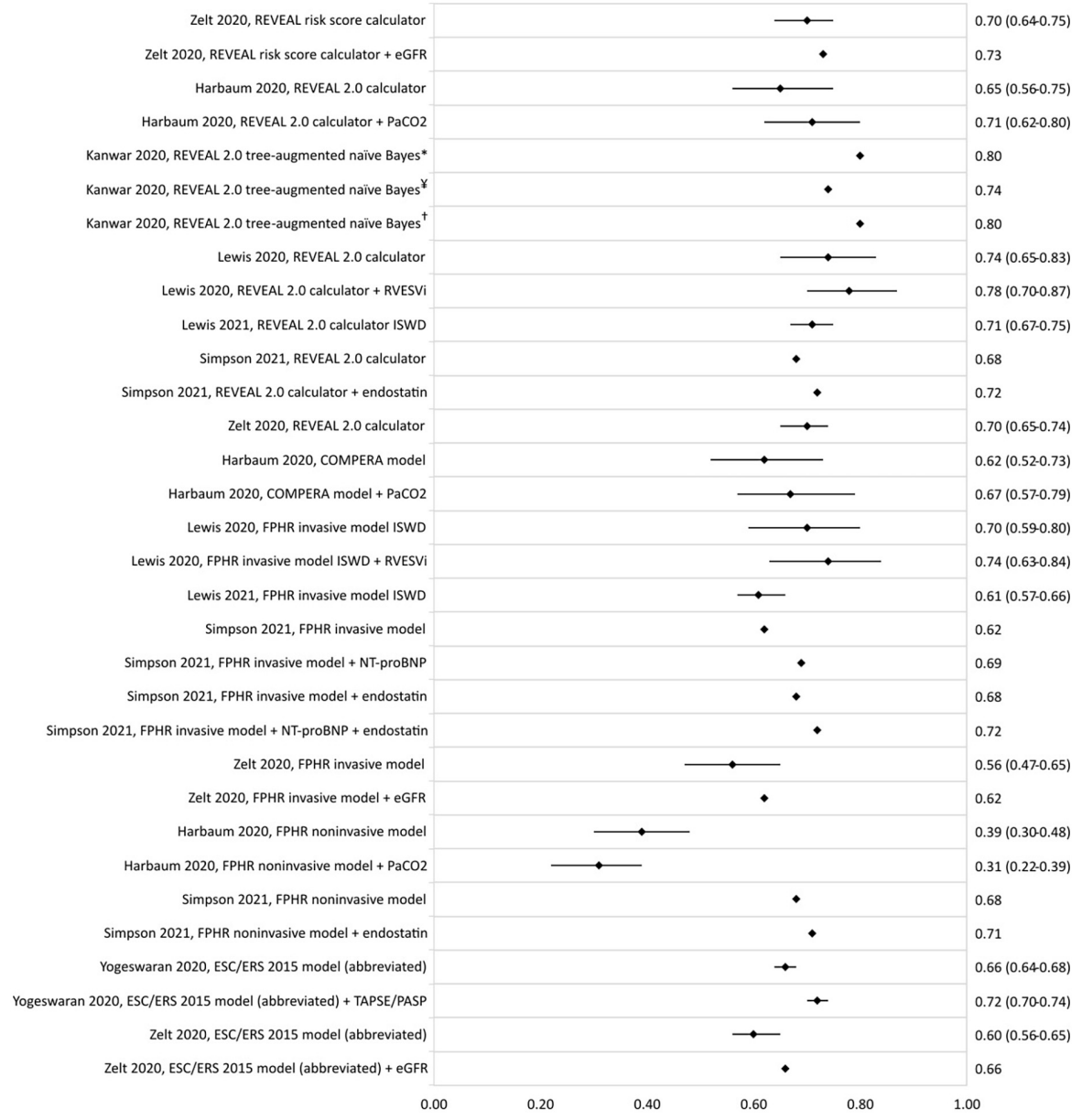

FIGURE 4
C-statistic (95% CI) of the enhancement of REVEAL and ESC/ERS 2015 guideline-based risk stratification models, as well as the c-statistic of the original model in the same population. eGFR, estimated glomerular filtration rate; PaCO2, arterial carbon dioxide partial pressure; RVESVi, right ventricular end-systolic volume index; ISWD, incremental shuttle walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; TAPSE/PASP, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio. *REVEAL cohort, ¥COMPERA cohort, and †PHSANZ cohort.

Risk of bias

The PROBAST results of the ROB analysis are presented in Table 8. The ROB for the domains participants, predictors, and outcome was low for almost every study. However, many studies were judged as having a high ROB based on the described analysis, causing an overall high ROB for nearly all studies. To differentiate between studies scoring poorly on one or two signaling questions and those failing on nearly all aspects of the analysis, the judgment is marked with one, two or three asterixis. These asterixis correspond to respective one to three, four to six, and seven or more negatively answered questions ("no" or "no information") out of nine for development studies and out of six for validation studies. There was low concern regarding applicability of models for participants, predictors, and outcome.

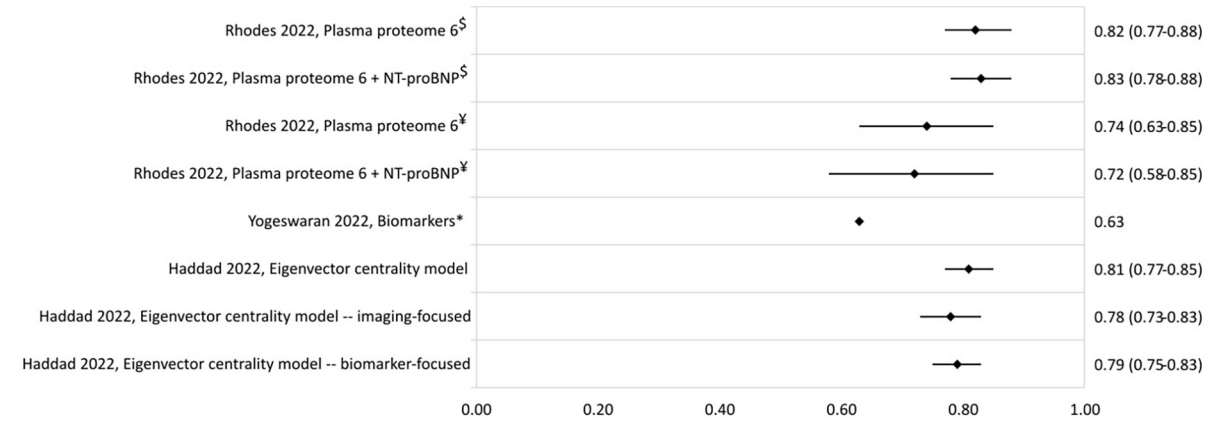

FIGURE 5
C-statistic (95% CI) of biomarker and eigenvector centrality risk stratification models. NT-proBNP, N-terminal-pro brain natriuretic peptide. $Derivation cohort, ¥validation cohort, *cohort includes PAH and chronic thromboembolic PH patients.

Discussion

In this systematic review we identified twenty different risk stratification models that have been proposed for adult PAH and only two for pediatric PAH. The REVEAL risk calculators are the most frequently validated models in literature, followed by the COMPERA model and FPHR invasive and non-invasive models. For the enhancement of existing risk stratification models, the FPHR invasive method and REVEAL 2.0 calculator have been studied most frequently. The non-invasive WHO-FC, 6MWD, and BNP/NT-proBNP, and the invasive mRAP, CI, and SvO_2 were found to be the variables that are most often used for the risk stratification of PAH. Reported c-statistics representing model predictive strength range from 0.39 to 0.77. Studies enhancing models by adding new variables report improvement of model strength.

Most risk stratification models include the non-invasive variables of WHO-FC, 6MWD, and BNP/NT-proBNP. The inclusion of these parameters in risk stratification may be due to the extensive studies on the prognostic value of these parameters, and stresses their important prognostic abilities in adult PAH patients. Based on the comparable predictive strength of non-invasive models and models including invasive parameters reported in three studies (19, 45, 46), a fully non-invasive risk stratification may be feasible. However, data supporting fully non-invasive risk stratification models are still scarce. Therefore, it may still be too early to set aside the invasive parameters included in most risk stratification models.

In the identified risk stratification models, different methods are used to combine cut-off scores of individual variables to determine the overall risk status. The three main definitions of risk are (1) the number of low risk criteria, (2) risk category based on an average score, and (3) risk category based on the total sum of the score. Furthermore, the risk stratification models can use weighted or unweighted variables. Risk stratification models using the number of low risk criteria (e.g., FPHR invasive and non-invasive method) or an average score (e.g., COMPERA and SPAHR models) do not take the weight of the variables into account for their determination of risk. This may lead to an underestimation or overestimation of patient risk. The REVEAL risk calculators were the only models found to consider the weighted values for individual variables in the calculation of risk. Variables that showed at least a twofold increase in hazard for mortality according to the multivariable Cox proportional hazard model were assigned two points, whereas variables with lower hazard received one point (10). This inclusion of variable weight in the risk estimation does appear to have an effect on the discriminatory ability of the model. C-statistics found in studies using the REVEAL risk calculators were, in general for most studies, higher (0.70–0.75) than those reported for COMPERA and FPHR models (0.62–0.69). These findings may favor the use of weighted risk scores instead of averages or number of low or high risk criteria in further development of risk stratification models.

Overall, the c-statistic of most studies was found to range between 0.6 and 0.8. Considering that a c-statistic of 0.5 indicates a poor prediction and 1.0 a perfect prediction, we may consider the current risk stratification models to have a moderate predictive ability. Whether or not this is sufficient enough to rely on for optimal treatment strategies can be debated. In the recently released 2022 ESC/ERS guidelines for the diagnosis and treatment of PH (4), the four-strata COMPERA 2.0 model of Hoeper et al. (22) using WHO-FC, 6MWD, and BNP/NT-proBNP is recommended for risk stratification at follow-up to guide treatment strategies in adult patients with PAH. The c-statistic for 1 year mortality of this four-strata model was reported to be 0.67 at baseline

TABLE 7 Variables used in pediatric risk stratification models.

Study	Model name	Definition of risk	Strata	Number of variables	WHO-FC	6MWD	NT-proBNP	RA area	Pericardial effusion	mRAP	CI	SvO_2	PVR	WHO group 1 subgroup	Male age > 60	Systolic BP	Heart Rate	% predicted DL_{CO}	ST2	TAPSE	Syncope	Height	BMI	mPAP/mSAP	PVRI	Acute vasoreactivity
Griffiths (44)	REVEAL 2.0 calculator	Risk score		11			or BNP																			
Griffiths (44)	REVEAL 2.0 calculator with REVEAL risk category	Risk category based on total score	5	11			or BNP																			
Griffiths (44)	REVEAL 2.0 calculator + ST2	Risk score		12			or BNP																			
Griffiths (44)	REVEAL 2.0 calculator with REVEAL risk category + ST2	Risk category based on total score	5	12			or BNP																			
Haarman (45)	WSPH 2013 model + SvO_2 + RA area	#low risk criteria	2	13																						
Haarman (45)	WSPH 2013 non-invasive model + RA area	#low risk criteria	2	7																						

WHO-FC, WHO functional class; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal-pro brain natriuretic peptide; RA area, right atrial area; mRAP mean right atrial pressure; CI, cardiac index; SvO_2, mixed venous oxygen saturation; PVR, pulmonary vascular resistance; BP, blood pressure; DL_{CO}, carbon monoxide lung diffusing capacity; ST2, soluble suppressor of tumorigenicity-2; TAPSE, tricuspid annular plane systolic excursion; BMI, body mass index; mPAP/mSAP, mean pulmonary arterial pressure/mean systemic arterial pressure ratio; PVRI, indexed PVR.

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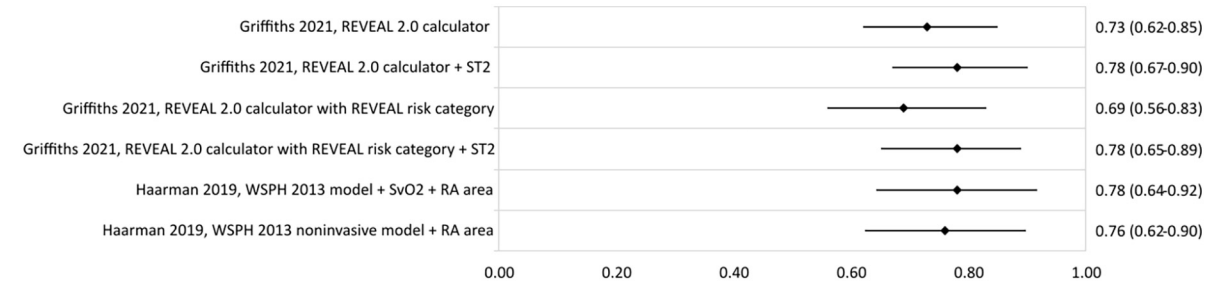

FIGURE 6
C-statistic (95% CI) of risk stratification models used in pediatric PAH. ST2, soluble suppressor of tumorigenicity-2; SvO2, mixed venous oxygen saturation; RA area, right atrial area.

and 0.73 at follow-up, in an external validation study by Boucly et al. (42). According to this, the authors would advocate that we should strive for improving current risk stratification models.

A possible approach for improving risk stratification models may be the addition of new parameters. The increase of the c-statistic in all enhancement studies, except for the addition of arterial carbon dioxide partial pressure to the FPHR non-invasive model (43), shows that the predictive strength of risk stratification models can be improved by adding imaging or serum biomarkers. Of all the enhancement studies, the addition of the right ventricular end-systolic volume index seems most promising (34). Prospective and external validation studies are needed to further establish the predictive value of enhanced models.

Furthermore, the use of risk stratification is not restricted to estimate risk at diagnosis or initiation of therapy. Also serial risk stratification every 3–6 months is proposed in order to use follow-up risk estimates to evaluate treatment response and to identify the need to escalate therapy (47). Recent reports show that risk stratifications may have a better discrimination of outcome at first follow-up RHC compared to baseline (48), and that changes in risk status are predictive of survival (49). Moreover, the addition of serial changes in NT-proBNP or right heart reverse remodeling (a combination of three echocardiographic parameters) increased the c-statistic of respective the eigenvector centrality model of Haddad et al. (41) (0.81–0.85) and the REVEAL 2.0 calculator (0.69–0.87) (50). As such the strength of risk stratification models may lie in serial assessments.

Data regarding the use of risk stratification models in pediatric PAH is extremely scarce. In this review, only two pediatric PAH studies were found, one based on the variables recommended by the WSPH 2013 pediatric task force and one based on the REVEAL 2.0 calculator. Nonetheless, risk stratification to guide treatment strategies is currently recommended also in the pediatric population. The updated guideline of the European Pediatric Pulmonary Vascular Disease for the diagnosis and treatment of pediatric pulmonary hypertension presents a risk score sheet for pediatric PH based solely on expert opinion (51). However, no validation yet exists and in the guideline it is stated that it is not clear which cut-offs should be used for the risk stratification variables. For this reason, Haarman et al. (45) in their study used cut-off values derived from separate prognosticator studies in children with PAH. Considering the reference class problem, which dictates that the prediction for the individual patient depends on the reference class the patient is assigned to, it is recommended to develop a risk stratification model with variable cut-offs and weights designed specifically for the pediatric population.

Nearly all studies included in this systematic review were judged to have a high ROB based on their analysis. This can be explained with closer observation of the analysis domain of PROBAST (16), the tool that was used to rate ROB. First, according to PROBAST, the number of events (death or death + transplant) per variable should be higher than 10 for development studies, and for validation studies at least 100 participants with the outcome are required. These criteria were met by approximately only half of the included adult studies. Since pediatric PAH is a rare disease, none of the included pediatric studies met the criteria for the number of participants, which shows the limitation of the applicability of PROBAST in a rare disease. Secondly, if continuous variables were dichotomized or categorized for the development of a model, according to PROBAST the model could have a high ROB. However, categorization forms the basis of risk stratification and thus many model development were rated to have a high ROB. For validation studies categorization of continuous variables was allowed if the cut-offs were similar to the original model. Third aspect in PROBAST is the inclusion of all enrolled participants in the analysis and the appropriate handling of missing data, since excluding patients with missing data may cause selection bias. Besides, selection bias is a reasonable risk of registry studies since there are nearly always missing data due to the data not being collected according to a protocol or for the research

TABLE 8 PROBAST results.

		ROB								Applicability						Overall			
		Participants		Predictors		Outcome		Analysis		Participants		Predictors		Outcome		ROB		Applicability	
Study	Model name	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val
Anderson (53)	REVEAL 2.0 calculator		–		+		+		–*		+		+		+		–		+
Austin (37)	REVEAL risk score calculator		+		+		+		–*		+		+		+		–		+
	Echocardiographic approach	+	+	+	+	+	+	–**	–*	+	+	+	+	+	+	–	–	+	+
Benza (10)	REVEAL risk score calculator	+	+	+	+	+	+	–**	–*	+	+	+	+	+	+	–	–	+	+
Benza (18)	REVEAL 2.0 calculator	+		+		+		–**		+		+		+		–		+	
	COMPERA model		+		+		+		–*		+		+		+		–		+
	FPHR invasive model		+		+		+		–*		+		+		+		–		+
Benza (19)	REVEAL Lite 2	+		+		+		–**		+		+		+		–		+	
Boucly (23)	FPHR invasive model	–		+		+		–***		+		+		+		–		+	
	FPHR non-invasive model	–		+		+		–***		+		+		+		–		+	
Boucly (42)	COMPERA model (abbreviated)		–		+		+		–*		+		+		+		–		+
	COMPERA 2.0 model		–		+		+		–*		+		+		+		–		+
Chang (54)	REVEAL Lite 2		+		+		+		–*		+		+		+		–		+
	COMPERA model		+		+		+		–*		+		+		+		–		+
	FPHR invasive model		+		+		+		–*		+		+		+		–		+
Chiu (24)	ESC/ERS 2015 model (abbreviated)	+		+		+		–***		+		+		+		–		+	
Dardi (25)	COMPERA model		+		+		+		–*		+		+		+		–		+
	FPHR invasive model		+		+		+		–*		+		+		+		–		+
	ESC/ERS 2015 model (abbreviated)	+		+		+		–**		+		+		+		–		+	
Ghio (38)	Echocardiographic approach	+		+		+		–**		+		+		+		–		+	
Griffiths (44)	REVEAL 2.0 calculator	–			+		+		–**		+		+		+		–		+
	REVEAL 2.0 calculator + ST2	–		+		+		–***		+		+		+		–		+	
Gong (55)	COMPERA model		+		+		+		–*		+		+		+		–		+
Haarman (45)	WSPH 2013 model + SvO_2 + RA area	+		+		+		–**		+		+		+		–		+	
	WSPH 2013 non-invasive model + RA area	+		+		+		–**		+		+		+		–		+	
Haddad (41)	Eigenvector centrality model	+		+		+		–**		+		+		+		–		+	
	Eigenvector centrality model–imaging-focused	+		+		+		–**		+		+		+		–		+	
	Eigenvector centrality model–biomarker-focused	+		+		+		–**		+		+		+		–		+	
Harbaum (43)	REVEAL 2.0 calculator		+		+		+		–*		+		+		+		–		+
	COMPERA model		+		+		+		–*		+		+				–		+
	FPHR non-invasive model		+		+		+		–*		+		+				–		+
	REVEAL 2.0 calculator + $PaCO_2$	+		+		+		–**		+		+		+		–			
	COMPERA model + $PaCO_2$	+		+				–**		+		+		+		–		+	
	FPHR non-invasive model + $PaCO_2$	+		+		+		–**		+		+		+		–		+	
Hjalmarsson (56)	SPAHR model		+		+		+		–*		+		+		+		–		+

(Continued)

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TABLE 8 (Continued)

		ROB								Applicability						Overall			
		Participants		Predictors		Outcome		Analysis		Participants		Predictors		Outcome		ROB		Applicability	
Study	Model name	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val
Hoeper (20)	COMPERA model	+		+		+		−**		+		+		+		−		+	
Hoeper (22)	COMPERA model (abbreviated)	−		+		+		−***		+		+		+		−		+	
	COMPERA 2.0	−		+		+		−***		+		+		+		−		+	
Imai (26)	ESC/ERS 2015 model (abbreviated)	+		+		+		−***		+		+		+		−		+	
Kanwar (19)	Tree-augmented naïve Bayes model of REVEAL 2.0	+	+	+	+	+	+	−**	−*	+	+	+	+	+	+	−	−	+	+
Kylhammar (64)	SPAHR model	+		+		+		−**		+		+		+		−		+	
Kylhammar (56)	SPAHR model		−		+		+		−*		+		+		+		−		+
Lee (52)	Scottish composite score	+	+	+	+	+	+	−**	−**	+	+	+	+	+	+	−	−	+	+
Lewis (34)	REVEAL 2.0 calculator		+		+		+	−*			+		+		+	−			+
	FPHR invasive model ISWD	+		+		+			−**	+		+		+			−	+	
	REVEAL 2.0 calculator + RVESVi	+		+		+			−**	+		+		+			−	+	
	FPHR invasive model ISWD + RVESVi	+		+		+			−**	+		+		+			−	+	
Lewis (62)	REVEAL 2.0 calculator ISWD	+		+		+		−*		+		+		+		−		+	
	FPHR invasive model ISWD	+		+		+		−**		+		+		+		−		+	
Li (27)	ESC/ERS 2015 model (abbreviated)	+		+		+		−***		+		+		+		−		+	
Mercurio (28)	FPHR invasive model		+		+		+		−**		+		+		+		−		+
	ESC/ERS 2015 model (abbreviated)	+		+		+		−***		+		+		+		−		+	
Mullin (58)	REVEAL risk score calculator		+		+		+		−*		+		+		+		−		+
Qu (59)	REVEAL risk score calculator		+		+		+		−*		+		+		+		−		+
Quan (46)	REVEAL 2.0 calculator		+		+		+		+		+		+		+		+		+
	REVEAL Lite 2		+		+		+		−*		+		+		+		−		+
	COMPERA model		+		+		+		+		+		+		+		+		+
	FPHR invasive model		+		+		+		−*		+		+		+		−		+
	FPHR non-invasive model		+		+		+		−*		+		+		+		−		+
Rhodes (39)	Plasma proteome 6	+	+	+	+	+	+	−*	−*	+	+	+	+	+	+	−	−	+	+
	Plasma proteome 6 + NT-proBNP	+	+	+	+	+	+	−*	−*	+	+	+	+	+	+	−	−	+	+
Simpson (35)	REVEAL 2.0 calculator		−		+		+		−*		+		+		+		−		+
	FPHR invasive model		−		+		+		−*		+		+		+		−		+
	FPHR non-invasive model		−		+		+		−*		+		+		+		−		+
	REVEAL 2.0 calculator + endostatin	−		+		+		−**		+		+		+		−		+	
	FPHR invasive model + NTproBNP	−		+		+		−**		+		+		+		−		+	
	FPHR invasive model + endostatin	−		+		+		−**		+		+		+		−		+	
	FPHR invasive model + NTproBNP + endostatin	−		+		+		−**		+		+		+		−		+	
	FPHR non-invasive model + endostatin	−		+		+		−**		+		+		+		−		+	

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TABLE 8 (Continued)

		ROB								Applicability						Overall			
		Participants		Predictors		Outcome		Analysis		Participants		Predictors		Outcome		ROB		Applicability	
Study	Model name	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val	dev	val
Sitbon (60)	REVEAL risk score calculator		+		+		+		−*		+		+		+		−		+
Vicenzi (63)	COMPERA model		−		+		+		−**		+		+		+		−		+
	FPHR invasive model		−		+		+		−**		+		+		+		−		+
	FPHR non-invasive model		−		+		+		−**		+		+		+		−		+
	COMPERA model + TAPSE/TRV or TAPSE/sPAP	−		+		+		−***		+		+		+		−		+	
	FPHR invasive model + TAPSE/TRV or TAPSE/sPAP	−		+		+		−***		+		+		+		−		+	
	FPHR non-invasive model + TAPSE/TRV or TAPSE/sPAP	−		+		+		−***		+		+		+		−		+	
Vraka (61)	REVEAL 2.0 calculator		+		+		+		−*		+		+		+		−		+
	COMPERA model		+				+		−*		+		+		+		−		+
	FPHR invasive model		+		+		+		−*		+		+		+		−		+
Wang (29)	ESC/ERS 2015 model (abbreviated)	+		+		+		−***		+		+		+		−		+	
Weatherald (48)	FPHR invasive model		+		+		+		−*		+		+		+		−		+
Xanthouli (30)	COMPERA model		+		+		+		−**		+		+		+		−		+
	FPHR non-invasive model		+		+		+		−**		+		+		+		−		+
	ESC/ERS 2015 model (abbreviated, non-invasive)	+		+		+		−***		+		+		+		−		+	
Xiong (31)	REVEAL risk score calculator		−		+		+		−*		+		+		+		−		+
	ESC/ERS 2015 model (abbreviated, non-invasive)	−		+		+		−**		+		+		+		−		+	
Yogeswaran (32)	ESC/ERS 2015 model (abbreviated)	+		+		+		−**		+		+		+		−		+	
	ESC/ERS 2015 model (abbreviated) + TAPSE/sPAP	+		+		+		−**		+		+		+		−		+	
Yogeswaran (40)	COMPERA model		+		+		+		−*		+		+		+		−		+
	Biomarker approach	+	+	+	+	+	+	−**	−*	+	+	+	+	+	+	−	−	+	+
Zelt (33)	REVEAL risk score calculator		+		+		+		−*		+		+		+		−		+
	REVEAL 2.0 calculator		+		+		+		−*		+		+		+		−		+
	FPHR invasive model		+		+		+		−*		+		+		+		−		+
	ESC/ERS 2015 model (abbreviated)	+		+		+		−**		+		+		+		−		+	
	REVEAL risk score calculator + eGFR		+		+		+		−**		+		+		+		−		+
	FPHR invasive model + eGFR		+		+		+		−**		+		+		+		−		+
	ESC/ERS 2015 model (abbreviated) + eGFR	+		+		+		−**		+		+		+		−		+	

PROBAST, Prediction model Risk Of Bias Assessment Tool; ROB, risk of bias; dev, development; val, validation; ST2, soluble suppressor of tumorigenicity-2; SvO_2, mixed venous oxygen saturation; RA area, right atrial area; $PaCO_2$, arterial carbon dioxide partial pressure; ISWD, incremental shuttle walk distance; RVESVi, right ventricular end-systolic volume index; NT-proBNP, N-terminal-pro brain natriuretic peptide; TAPSE/TRV, tricuspid annular plane systolic excursion/tricuspid regurgitation velocity ratio; TAPSE/sPAP, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio; eGFR, estimated glomerular filtration rate. +Indicates low ROB/low concern regarding applicability; −indicates high ROB/high concern regarding applicability; *1–3, **4–6, ***≥ 7 negatively answered questions.

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question at hand. Fourth, multiple studies did not report c-statistic or AUROC, where PROBAST demands reporting of both calibration and discrimination measures. Information on model overfitting and optimism in model performance was also often not described. Finally, the weights of the variables in the final model had to correspond to the results from the reported multivariable analysis. As discussed earlier, models defining risk by the number of low risk criteria or based on an average score do not take the weight of a variable into account, and thus these studies were also at high ROB.

This study has several limitations. Not all included studies reported a c-statistic, which may have caused a bias in the judgment of the prognostic value of the models. The patients included in studies performed more recently were receiving treatment according to the risk stratification-based treatment algorithms. This may have influenced the outcome of those patients, which could have affected the prognostic value of risk stratification models of these studies. No meta-analysis was performed limiting direct conclusions on which model performs best. In order to keep focus, the studies concerning serial risk stratification were disregarded, limiting the ability to discuss the value of serial follow-up risk stratification.

For future purposes, it is recommended to perform prospective validation studies of the risk stratification models since now only retrospective studies of risk stratification exist. Studies developing new models or validating existing models should consider including both calibration and discrimination measures as both are needed to thoroughly describe the performance of the model. Furthermore, an individual patient data systematic review is recommended to define which risk stratification model has the best performance.

Conclusion

This systematic review contributes to our current knowledge on risk stratification in PAH and emphasizes the very limited presence of studies reporting risk stratification in pediatric PAH. The variables found to be used the most frequently in risk stratification models are WHO-FC, 6MWD, NT-proBNP (or BPN), mRAP, CI, and SvO_2. The prognostic value of current risk stratification models is moderate to good, at best, and may be improved by adding new imaging and serum biomarkers, using weighted risk stratification variables, and adding changes in clinical parameters at serial risk stratification during follow-up. Moreover, there is a need for prospective validation of risk stratification models and more research into risk stratification for pediatric PAH has to be pursued.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

All authors contributed to the development of the research question and selection criteria. CL and SW developed the search strategy and drafted the initial manuscript. Title-abstract and full-text screening was performed by CL and JD, where RB was consulted in case of disagreement. Data extraction, risk of bias, and data analysis was performed by CL in consultation with RB and JD. RB and JD reviewed and revised the manuscript.

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Conflict of interest

RB reports that the University Medical Center Groningen contracts with Janssen, Ferrer, and MSD, for advisory board and steering committee activities, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1035453/full#supplementary-material

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EDITED BY
Stephanie Handler,
Medical College of Wisconsin, United States

REVIEWED BY
Connie Miller,
Centers for Disease Control and Prevention (CDC), United States
Peter Oishi,
University of California, United States

*CORRESPONDENCE
Ivonne Wieland
wieland.ivonne@mh-hannover.de
Georg Hansmann
georg.hansmann@gmail.com

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Acquired von Willebrand syndrome (AVWS) type 2, characterized by decreased high molecular weight multimers, is common in children with severe pulmonary hypertension (PH)

Ivonne Wieland[1]*, Franziska Diekmann[2], Julia Carlens[3], Laura Hinze[1], Katharina Lambeck[1], Thomas Jack[2] and Georg Hansmann[2]*

[1]Department of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany, [2]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany, [3]Department of Pediatric Pulmonology, Allergology, and Neonatology, Hannover Medical School, Hannover, Germany

Background and objectives: Emerging evidence suggests that increased degradation of von Willebrand factor and decrease in high molecular weight multimers occurs in patients with pulmonary hypertension (PH). However, the link between acquired von Willebrand Syndrome (AVWS) type 2 and PH remains poorly understood.

Material and methods: We retrospectively evaluated the charts of 20 children with PH who underwent bilateral lung transplantation (LuTx) between 2013 and 2022. Von Willebrand variables were determined in 14 of these patients; 11 patients had complete diagnostics including multimer analysis.

Results: We confirmed AVWS in 82% of the children studied (9 of 11 patients by multimer analysis). The two remaining patients had suspected AVWS type 2 because of a VWF:Ac/VWF:Ag ratio of <0.7. Platelet dysfunction or suspicion of VWD type 1 were found in two separate patients. All but one of the 14 children with severe PH had a coagulation disorder. Most patients (9 proven, 2 suspected) had AVWS type 2. Notably, 3 of 5 patients (60%) with normal VWF:Ac/VWF:Ag ratio >0.7 had abnormal VWF multimers, indicating AVWS type 2. Hemostatic complications were observed in 4 of 12 (33%) patients with VWS and 3 of 6 (50%) patients without diagnostics and therapy.

Conclusion: For children with moderate to severe PH, we recommend systematic analysis of von Willebrand variables, including multimer analysis, PFA-100 and platelet function testing. Awareness of the diagnosis "AVWS" and adequate therapy may help to prevent these patients from bleeding complications in case of surgical interventions or trauma.

KEYWORDS

acquired von willebrand syndrome (AVWS), pulmonary hypertension, bleeding risk, high molecular weight multimers, children

Introduction

Von Willebrand factor (VWF) is a protein, which is required for adhesion, playing an important role in hemostasis. Various hereditary types (type 1–3) of von Willebrand disease (VWD) are described, in which mainly a reduction of VWF and/or VWF-multimers is involved (1). According to published data on the prevalence of VWD, hereditary VWD is found in up to 1% of the population, but the proportion of patients with VWD with clinical relevance is even smaller (one in 10,000 people) (1). VWD type 1 with reduced VWF, is the most common type (70%–80%), followed by type 2 that is characterised by reduction or loss of large VWF multimers (20%–25%), and type 3 with a complete loss of VWF (<1%–5%) (1, 2). Acquired von Willebrand Syndrome (AVWS) was reported to have a prevalence of 0.04% to 0.13% in the population (3). Generally, AVWS is associated with an underlying disorder. According to the International Society on Thrombosis and Haemostasis (ISTH) registry (4) and a recent report (5), the most common conditions associated with AVWS are: lymphoproliferative/haematological malignancy (48%), cardiovascular (21%), myeloproliferative (15%), other neoplastic (5%) and autoimmune disorders (2%–5%) or various other causes (plasma-mediated hyperfibrinolysis, glycogen storage disease, uremia, hypothyroidism) (<10%) (4, 5).

In the paediatric population, AVWS tends to be underdiagnosed and often unknown. However, data on AVWS in childhood are rare and mostly case reports or small case series. Most data are reported for AVWS in pediatric patients with congenital heart diseases (6–14).

Acquired AVWS as type 2A is especially common in adult patients with aortic valve stenosis (vAS) (15). 67%–92% of patients with severe aortic stenosis (vAS) are reported to develop AVWS, and 21% of those patients suffer from bleedings (16). Pathophysiologically, it was assumed that the development of AVWS in vAS is caused by the acceleration of blood flow at the aortic valve, resulting in shear stress for large plasma proteins like VWF, leading to consecutive proteolytic cleavage of VWF and a decrease or loss of the high molecular weight multimers (HMWMs). In addition to aortic stenosis, AVWS was reported for instance in hypertrophic obstructive cardiomyopathy (HOCM), tetralogy of Fallot, pulmonary hypertension and mitral regurgitation (17).

According to the World Symposium on Pulmonary Hypertension (WSPH, 2018), pulmonary hypertension (PH) is a condition that is divided into 5 subgroups (18–20).

The pathobiology of pulmonary arterial hypertension (PAH) is a complex and multifactorial process, in which peripheral artery loss and obstructive vascular remodeling cause a rise in pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR), resulting in progressive right heart failure and death (21). Inflammation, delayed shear adaptation and endothelial cell dysfunction seem to play crucial roles in this process (22–25). Wall shear stress-dependent changes in pulmonary arterial lumen diameter were found to be a persistent remodeling response (26).

Especially in young patients, the etiology of PH (groups 1–5) is very heterogeneous across the different age groups, but most frequently associated with congenital heart disease (CHD; group 1 PH = pulmonary arterial hypertension), followed by developmental lung disease (group 3 PH; mainly bronchopulmonary dysplasia) and so-called idiopathic PAH forms (18, 19, 21). The estimated incidence for idiopathic PAH (IPAH)/heritable PAH (HPAH) and (non-transient) CHD-associated PAH is 0.7 and 2.2/million, and the estimated prevalence is 4.4 and 15.6/million children, respectively. (19).

From the late 1980s, emerging evidence suggested that PAH patients have increased degradation of VWF and a decrease in high molecular weight multimers, and/or platelet dysfunction, which are typical findings of AVWS type 2 (27). Abnormal flow or shear stress through the pulmonary vessels has been suggested to cause PAH in 1995 (28). A study on 30 PAH patients showed that those patients with abnormalities in VWF had a reduced 1-year survival rate compared with those with normal VWF (29).

Apart from isolated cases, such as the case report on an adolescent woman with PAH and menorrhagia suffering from AVWS type 2 (30), very little data on AVWS in pediatric PH has been published so far. In another cohort of 16 patients with CHD, 5 had PAH. All of them suffered from AVWS type 2 and presented with bleeding symptoms such as epistaxis, menorrhagia or gum bleeding (31). Surprisingly, in a small study on 8 children with PAH, all of them had AVWS type 1 with a normal multimer analysis differing from other reports describing an association with abnormalities in VWF or AVWS type 2 (32).

In this retrospective study, we analyzed the von Willebrand variables in all children with severe PH and right ventricular (RV) failure undergoing lung transplantation (LuTx) at Hannover Medical School between December 2013 and February 2022. We hypothesized that most end-stage PH patients have evident AVWS type 2 that is relevant to patient management perioperatively (e.g., VWF supplementation).

Material and methods

We retrospectively evaluated the charts of 20 children with PH undergoing lung transplantation at Hannover Medical School between December 2013 and February 2022 for von Willebrand variables (von Willebrand factor activity (VWF:Ac); von Willebrand factor antigen (VWF:Ag), multimers) and, when performed, for platelet function analysis (**Figure 1**).

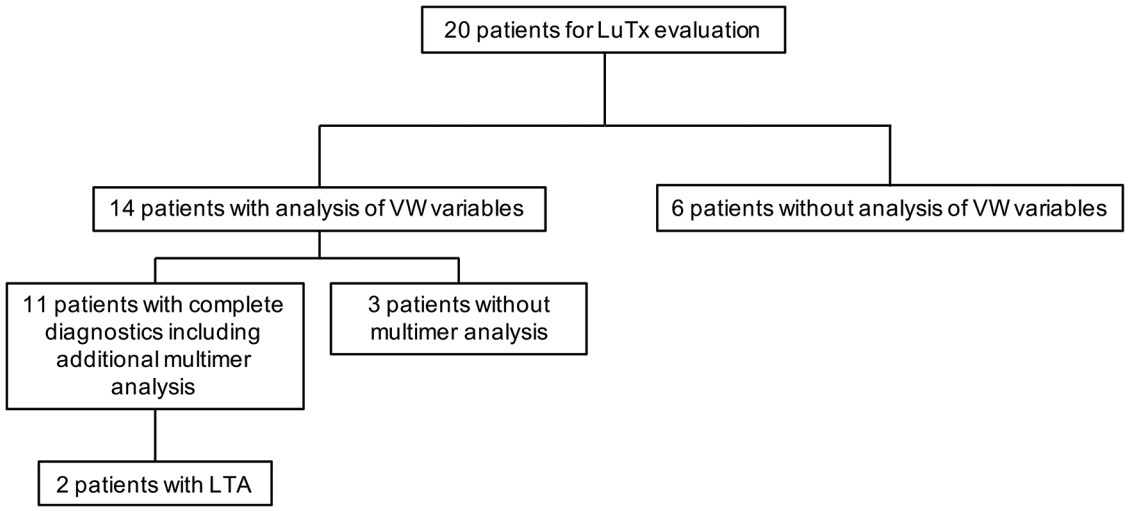

FIGURE 1
Diagnostic workup. The indicated VW variables include von Willebrand factor activity (VWF:Ac) and von Willebrand factor antigen (VWF:Ag). LTA, light transmission aggregometry; LuTx, lung transplantation; VW, von Willebrand.

Measurement of von Willebrand parameters were performed once during evaluation for lung transplantation in the central laboratory of MHH. VWF:Ag and VWF:Ac were determined in the Siemens instruments tubimetricly. PFA-100 was measured on COLL/EPI and COLL/ADP membranes on a Siemens instrument. For platelet function analysis, light transmission aggregometry (LTA, so called "Born-Aggregation") was performed in the APACP 4S Plus/DiaSys instrument.

Von Willebrand Multimer analysis was done externally by the laboratory AMEDES, Hamburg, following standardized protocols.

Patients with a VWF:Ac/VWF:Ag ratio <0.7 are suspected of having VWS type 2 according to the ASH guidelines (33). AVWS type 2 was confirmed with a loss of largest and reduction of large multimers in multimer analysis independent of the VWF:Ac/VWF:Ag ratio.

Von Willebrand variables (VWF:Ag and/or VWF:Ac) ≤ 50% were classified as suspected VWD type 1. We cannot differ between congenital or acquired.

Von Willebrand variables, at least in our laboratory, were determined in only 14 of the 20 patients. Twelve of these 14 patients were female. The mean age at transplantation was 10.9 years (range 1.9–21.3 years) (**Table 1**, **Supplementary Table S1**).

Nineteen patients were classified as group 1 PH (idiopathic ($n = 8$) or heritable PAH ($n = 5$), PAH-CHD (PAH associated with congenital heart disease, n = 3) and PVOD/PCH [pulmonary veno-occlusive disease PVOD)/pulmonary capillary hemangiomatosis (PCH), n = 3] and one as group 3 PH (PH associated with developmental lung disease) (**Table 1**, **Supplementary Table S1**).

All patients underwent ECMO peri transplantation. The management of PAH patients undergoing LuTx at our center using veno-arterial ECMO (VA-ECMO) support has previously been published (34, 35). Only patients with known or suspected VWS received VWF supplementation during VA-ECMO support pre and post LuTx, no patient without known VWS. We further identified complications related to hemorrhage and thromboembolic events in all 20 pediatric patients pre and post lung transplantation (LuTx).

Results

Analysis of von Willebrand variables and platelet function

Von Willebrand variables (VWF:Activity (VWF:Ac) and VWF:Antigen (VWF:Ag)) in our locale laboratory were determined in 14 of these patients, but the diagnostic workup was complete in only 11 patients and confirmed by multimer analysis (**Figure 1**).

In these 14 patients, we could find 9 (64%) with confirmed AVWS type 2, 2 (14%) with suspected AVWS type 2, 1 (7%) platelet dysfunction and 1 (7%) with suspected VWD type 1 (without excluded type 2 because of missing multimer analysis) (**Figure 2**, **Table 2**).

Eight of the 14 patients (57%) were suspected for AVWS type 2 due to a ratio of <0.7. In six of these patients, multimer analysis was performed and all of them (100%) demonstrated a decrease or loss of HMWM, which is typical of AVWS type 2. The

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TABLE 1 Characteristics of the 20 PH patients studied.

Patients #1–20	PH patients $N = 20$
Demographics	
Age – years (range)	10.9 ± 1.2 (1.9–21.3)
Sex, Female – *n* (%)	16 (80%)
Height – m	1.4 ± 0.1
Weight – kg	32.3 ± 3.8
BSA – m^2	1.1 ± 0.1
Clinical Diagnosis	
PH Group 1 – *n*	19
1.1 IPAH	8
1.2 HPAH (BMPR2, *n* = 4; TBX4, *n* = 1)	5
1.4.4 PAH-CHD	3
1.6 PVOD/PCH	3
PH Group 3 – *n*	1
WHO Functional Class	3.6 ± 0.1
NTproBNP – ng/L	3065.9 ± 814.8
Invasive Hemodynamics	
mRAP – mm Hg, *n* = 16	8.1 ± 1.0
RVEDP – mm Hg, *n* = 15	12.3 ± 0.7
mPAP – mmHg, *n* = 17	74.3 ± 4.2
mPAP/mSAP, *n* = 16	1.1 ± 0.0
PVRi – WU·m^2, *n* = 17	24.0 ± 2.4
PVR/SVR, *n* = 17	1.3 ± 0.1
Qsi – L/min/m^2, *n* = 16	3.6 ± 0.5

Values are presented as mean ± SEM. If the patient has a mutation that is associated with PAH, he/she belongs to group 1.2 PH (HPAH). One patient (listed here as IPAH) may also be classified as PAH-CHD (group 1.4.4). The serum N-terminal prohormone of brain natriuretic peptide (NTproBNP) concentrations are the last measurements prior to lung transplantation (LuTx). Only catheterization data from the previous 12 months prior to LuTx are shown. One patient did not undergo catheterization at all and two patients did not have a cardiac cath within the 12 months before LuTx. BSA, body surface area; cath, catheterization; CHD, congenital heart disease; HHT, hereditary hemorrhagic telangiectasia; HPAH, hereditary PAH; IPAH, idiopathic PAH; LuTx, lung transplantation; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; mSAP, mean systemic arterial pressure; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PVOD, pulmonary venoocclusive disease; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; Qsi, systemic flow index; RVEDP, right ventricular end-diastolic pressure; SVR, systemic vascular resistance; WHO, World Health Organization.

remaining two patients were classified as suspected AVWS type 2 because of missing multimer analysis.

Six of the 14 patients (43%) had a normal VWF:Ac/VWF:Ag ratio (>0.7). In five of them, multimer analysis was performed. Despite a normal VWF:Ac/VWF:Ag ratio of >0.7, 3 of these 5 patients (60%) had a decrease or loss of HMWM, indicating these patients suffer from AVWS type 2. In 2 of these 3 patients, PFA-100 was performed and was highly increased (>300s).

Of the 2 patients with excluded AVWS type 2 by multimer analysis, one patient (patient 11) had pathological results in platelet function analysis. Despite normal platelet numbers, PFA-100 was highly increased (>300s) and in LTA, aggregations of each stimulus (ADP 10 µM, adrenalin 5 µM, collagen 5 µg/ml and ristocetin 1.0 mg/ml) were decreased, indicating platelet dysfunction in this patient. Due to the slightly reduced von Willebrand variables, patient 8 is suspected for at least VWD type 1, without fully excluded type 2 because of missing multimer analysis.

Bleeding complications and thromboembolic events peri-LuTx

Four patients were bridged to transplantation on veno-arterial ECMO. All patients were transplanted on cardiopulmonary bypass or ECMO and all but one (patient number 6) remained on planned ECMO support after transplantation. Patients on ECMO and/or cardiopulmonary bypass received anticoagulation. Patients with known or suspected VWS were treated preventively with VWF containing concentrate during VA-ECMO to prevent bleeding complications.

We observed bleeding complications (hematothorax) in 4 patients (patients 5, 16, 18, 19) in the first days after transplantation. Two (2 of 12; 17%) of these occurred in patients with confirmed/suspected AVWS and two (2 of 6; 33%) in patients without extended hemostatic diagnostic work-up. One additional patient (number 1) suffered from hematothorax because of cannula dislocation during emergency ECMO cannulation before transplantation. Because the bleeding was caused by cannula dislocation, we do not include this patient in the group with bleeding complications.

We observed thromboembolic complications in 6 patients (patients 2, 5, 12, 13, 16, 18): four developed emboli after lung transplantation with ischemia in limb arteries during ECMO therapy or shortly after ECMO explantation, one suffered an infarction of the A. cerebri media on ECMO and one suffered a spinal cord ischemia before lung transplantation while on bridge-to-transplantation ECMO support. Three (3 of 12; 25%) of these occurred in patients with confirmed/suspected AVWS and three (3 of 6; 50%) in patients without extended hemostatic diagnostic work-up.

Both bleeding and thromboembolic events occurred in 3 patients [1 with AVWS (patient 16) and 2 without diagnostic workup (patients 5, 18)]. Details are summarized in **Table 3**.

Discussion

The detection of potential bleeding disorders is important in patients with advanced cardiovascular and pulmonary disease,

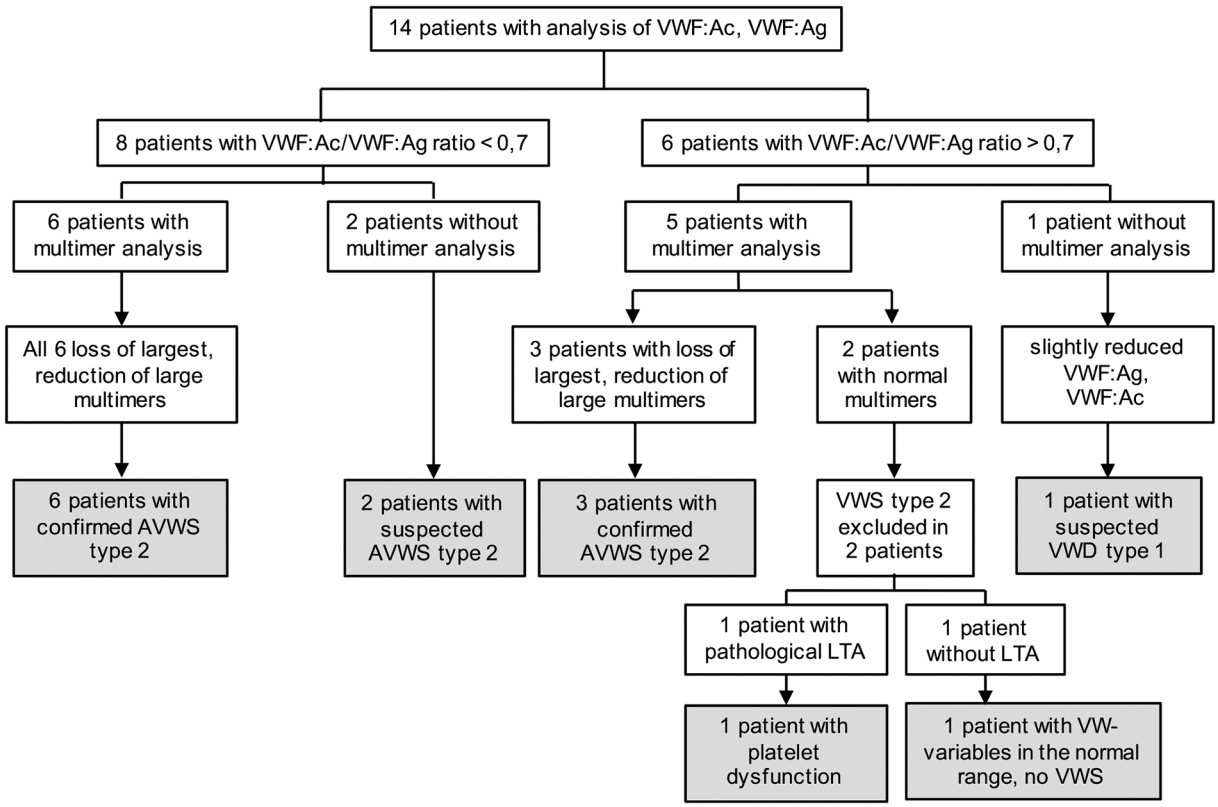

FIGURE 2
Results of diagnostic workup.
AVWS, acquired von Willebrand syndrome; LTA, light transmission aggregometry, VWF: Ac, von Willebrand factor activity; VWF: Ag, von Willebrand factor antigen; VWS, von Willebrand syndrome.

including group 1 PH (PAH) and group 3 PH, especially if those patients undergo major surgery such as lung transplantation or creation of endogenous Potts shunt (35–37).

In all but one of the 14 children with severe PH from our cohort with diagnostics, we detected a coagulation disorder. AVWS type 2 (confirmed or suspected: 11/13; 85%) was the most common coagulation disorder. We found confirmed AVWS in 9 of 14 (64%) patients [9 of 11 children with complete workup (82%)]. Two more patients were suspected for AVWS type 2 because of VWF:Ac/VWF:Ag ratio <0.7. Two others suffered from platelet dysfunction (n = 1) or were suspected of having at least VWS type 1 (n = 1; without fully excluded type 2 because of missing multimer analysis). In one patient without coagulation abnormality, platelet function analysis was missing.

Multimer analysis is proving AVWS type 2 and should be performed in all patients if AVWS type 2 is suspected. However, multimer analysis is a time-consuming method only available in some specialized laboratories. For urgent clinical questions other tests are required that initially indicate the presence of AVWS type 2 - the VWF:Ac/VWF:Ag ratio <0.7 (33). In all our patients with a VWF:Ac/VWF:Ag ratio <0.7, multimer analysis confimed AVWS type 2. However, 60% of the patients with a normal VWF:Ac/VWF:Ag ratio >0.7 also had a decrease or loss of HMWM, indicating these patients suffer from AVWS type 2 too. This finding is in line with other reports (13, 38). For instance, Icheva et al. reported for their cohort of patients with CHD a very high specificity (100%) of the ratio VWF:RCo/VWF:Ag (RCo; Ristocetin-Cofactor) to detect an AVWS, but a very low sensitivity (38%). (13). In contrast, Tiede et al. found a sensitivity of 86% (38). Because of the relatively low sensitivity of the VWF: Ac/VWF:Ag ratio, some patients with AVWS type 2 can be missed using only this method. Possibly, this diagnostic uncertainty could be reduced by additional analysis of PFA-100, for which a sensitivity of >90% has been described for VWD type 2 (39). Concerning the sensitivity and specificity of the different tests, further investigations are necessary.

The pathophysiology of AVWS in PH seems to be comparable to that in patients with aortic stenosis and may also result from increased shear stress for large plasma proteins like VWF. The latter leads to consecutive proteolytic cleavage of VWF and a decrease or loss of HMWMs (24).

TABLE 2 Results: laboratory results and hemostaseological diagnosis.

ID	VW-Variables before LuTx					Platelet function	Diagnosis
	VWF: Ac	VWF: Ag	Ratio Ac/Ag	PFA-100	Multimer analysis	LTA	
2	139.8	260	0.54	N/A	N/A	N/A	**Suspected AVWS type 2**
4	98.7	149	0.66	N/A	Relative reduction of large multimers	N/A	**AVWS type 2**
7	49.7	73	0.68	N/A	N/A	N/A	**Suspected AVWS type 2**
8	51.5	46	1.1	N/A	N/A	N/A	**suspected VWD type 1**
9	129	80	1,6	>300	Loss of largest, reduction of large multimers	Pathological	**AVWS type 2**
10	63	46	1.4	N/A	Loss of largest, reduction of large multimers	N/A	**AVWS type 2**
11	62	71	0.87	>300	*Normal*	Pathological	**platelet dysfunction**
12	99	151	0.63	N/A	Loss of largest, reduction of large multimers	N/A	**AVWS type 2**
14	32	54	0.59	N/A	Loss of largest, reduction of large multimers	N/A	**AVWS type 2**
15	37.4	58.6	0.63	N/A	Loss of largest, reduction of large multimers	N/A	**AVWS type 2**
16	29	37	0.78	>300	Loss of largest, reduction of large multimers	N/A	**AVWS type 2**
17	62.6	79.7	0.78	N/A	Loss of largest, reduction of large multimers	N/A	**AVWS type 2**
19	53.8	77.2	0.69	N/A	Loss of largest, reduction of large multimers	N/A	**AVWS type 2**
20	83.7	87.4	1	N/A	*Normal*	N/A	No VWS

AVWS, acquired von Willebrand syndrome; N/A, not available; PFA-100, platelet function analyzer; VWF: Ac, von Willebrand factor activity; VWF: Ag, von Willebrand factor antigen; VWS, von Willebrand syndrome.

We found a higher proportion of patients with AVWS type 2 in our pediatric cohort with end-stage PH than previously reported (32). In the small study of Pelland-Marcotte, 8 of 14 patients with PAH have shown bleeding symptoms and/or laboratory abnormalities but with normal VW-multimers, surprisingly excluding type 2 AVWS. One of these patients was in NYHA functional class (FC) III and underwent lung transplantation. The 7 other patients were in NYHA FC I ($n = 4$), NYHA FC I-II ($n = 2$) and NYHA II-III ($n = 1$). In contrast, we only analyzed patients with severe PAH immediately prior to LuTx. Therefore, the results of our study may indicate that the risk of AVWS increases with the severity of PAH. This observation is in line with the much earlier report of Lopes et al., demonstrating that patients with PAH and abnormalities in circulating VWF have a reduced 1-year-survival (29).

The clinical importance of an increased bleeding risk in patients with AVWS is the subject of a controversial discussion (15, 40–42). On the one hand, published data show that AVWS is not or only mildly associated with a relevant bleeding risk in adults with aortic stenosis (16). No increased bleeding tendency was reported, neither in daily life nor during surgery of aortic valve stenosis in adults (40–42). On the other hand, a meta-analysis of patients with AVWS, including data from two different registries, demonstrated an increased rate of patients (77%) with bleeding diathesis in the subgroup of patients with underlying cardiovascular disease (4). However, data on the prevalence and clinical bleeding tendency in PH patients with AVWS, especially in children with PH, are missing. Recently, a report on a patient with end-stage PAH and a major bleeding following reverse Potts shunt procedure was published (43). Two other small clinical studies showed that 4 of 5 patients with PAH (31) and 7 of 8 patients with PH (32) suffered from bleeding symptoms (31, 32), suggesting a high percentage of bleeding in VWS associated with PAH. The most common bleeding problems included epistaxis, menorrhagia, and perioperative bleedings like hereditary VWD (30–32, 43).

Re-Thoracotomy for major bleeding (hematothorax) is a major and common complication in the first hours and days after lung transplantation in young patients with severe PAH. In 117 lung transplanted pediatric patients from our center (including children with pulmonary hypertension and other diagnoses), 13 (11.1%) required re-thoracotomy for hematothorax after transplantation (35). Based on our findings and previous experience (35, 36), we substitute VWF containing concentrate in all PAH patients with confirmed or suspected VWS type 1 or 2, prior to, during and after invasive procedures or surgery, and also during VA-ECMO while being heparinized.

In the group of patients with VWS, 4 of 12 patients (33%) suffered from hemostatic complications (2 embolisms, 1 hematothorax, 1 both). In the group without extended diagnostics, three of six patients (50%) had hemostatic complications (1 thromboembolism and 2 both, thromboembolisms and hematothoraces). These complications were usually in temporal relation to the ECMO support. The etiology of these complications is likely multifactorial. Patients on VA-ECMO support require anticoagulation with heparin but were all substituted with coagulative agents at the same

TABLE 3 Diagnosis and hemostaseologic complications peri-translantation.

ID	Diagnosis	Hemostaseological Complications peri-transplantation
1	N/A	**Hematothorax due to cannula dislocation** during emergency ECMO cannulation before LuTx listing
3	N/A	None
5	N/A	**Hematothorax** (after central ECMO cannulation) after transplantation, **Stroke** of A. cerebri media post LuTx on ECMO
6	N/A	None
13	N/A	**Embolus and leg ischemia** after ECMO explantation requiring second embolectomy post LuTx
18	N/A	**Hematothorax after transplantation;** **spinal cord ischemia** with bilateral leg paralysis on pre-LuTx ECMO
20	No VWS	None
11	Platelet dysfunction	None
2	**Suspected AVWS type 2**	**Embolus** in right A. iliaca post LuTx after ECMO
4	**AVWS type 2**	None
7	**Suspected AVWS type 2**	None
8	**Suspected VWD type 1**	None
9	**AVWS type 2**	None
10	**AVWS type 2**	None
12	**AVWS type 2**	**Embolus** in right A. brachialis post LuTx after ECMO
14	**AVWS type 2**	None
15	**AVWS type 2**	None
16	**AVWS type 2**	**Hematothorax after transplantation**; **Embolisms** Aa femoralis, radialis and ulnaris left after ECMO explantation requiring second embolectomy, Pulmonary embolism post LuTx.
17	**AVWS type 2**	None
19	**AVWS type 2**	**Bilateral hematothorax** post LuTx on ECMO

N/A, not available; AVWS, acquired von Willebrand syndrome; VWS, von Willebrand syndrome, ECMO, extracorporal membrane oxygenation. A, arteria.

time. Both bleedings and thrombotic events are well known complications in ECMO treatment. Despite substitution with VWF containing concentrate to improve hemostasis, we did not observe an increase of thromboembolic events in the group with VWS (25% vs. 50%). Due to the small number of patients, a statistic analysis between AVWS and clinical outcome was not possible. Further investigations are necessary to determine whether hemostatic diagnostics can improve clinical outcome.

The limitation of our study is the relatively small number of patients. However, these patients showed a low heterogeneity and a comparable disease severity at the time of analysis shortly before LuTx.

Conclusion

Due to the high risk of bleeding complications in patients with severe PH, we recommend analysis of von Willebrand variables (VWF:Ag, VWF:Ac), multimer analysis, PFA-100 and platelet function testing [light transmission aggregometry (LTA, "Born-Aggregation")] in all patients with severe PH. At least, multimer analysis is evidential for AVWS type 2 and should be performed in all of these patients. Early suspicion of evident AVWS type 2, before receiving the result of the mandatory multimer analysis, should be raised in case of a VWF:Ac/VWF:Ag ratio <0.7 and a prolongation of PFA-100. Of note, because of relatively low sensitivity of this ratio, some patients with AVWS could be missed. The recommendation to use the VWF:Ac/VWF:Ag ratio is for practical reasons, because multimer analysis is a time-consuming method and not available in most hospitals.

Early diagnosis of AVWS type 2 in critically ill PH patients undergoing ECMO cannulation and/or major surgery could give the health care providers the opportunity to treat or prevent potential hemorrhagic events and may improve the patients' safety and outcomes.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Author contributions

The authors meet the following criteria: 1. Substantial contributions to conception and design, 2. Acquisition of samples, 3. Analysis of data, 4. Interpretation of data, 5. Drafting the article or revising it critically for important intellectual content, 6. Final approval of the version to be published. IW 1, 3–6; FD 3, 5, 6; JC 1–6; LH 3, 5, 6; KL 3, 5, 6; TJ 3–6; GH 1–6. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1012738/full#supplementary-material.

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EDITED BY
Catherine Avitabile,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
Neil Patel,
Royal Hospital for Children, United Kingdom
Gabriel Altit,
McGill University, Canada

*CORRESPONDENCE
Liezl Domingo
Liezl.Domingo@hsc.utah.edu

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Novel use of riociguat in infants with severe pulmonary arterial hypertension unable to wean from inhaled nitric oxide

L. T. Domingo[1]*, D. D. Ivy[2], S. H. Abman[2], A. M. Grenolds[2], J. T. MacLean[2], J. A. Breaux[2], K. J. Minford[1] and B. S. Frank[2]

[1]Department of Pediatrics, Primary Children's Hospital, University of Utah, Salt Lake, UT, United States, [2]Department of Pediatrics, Children's Hospital of Colorado, University of Colorado, Aurora, CO, United States

Introduction: Riociguat, an oral soluble guanylate cyclase stimulator, has been approved for use in adults with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension. However, there is limited data on its therapeutic use in children.

Case Presentation: We report the case of two infants with severe suprasystemic pulmonary hypertension who were successfully treated with riociguat after failure to wean off inhaled nitric oxide (iNO) despite combination PAH therapy. Case 1 is a 6-month-old term male with TBX4 deletion who presented with severe hypoxemic respiratory failure and severe PAH immediately after birth. Initial cardiac catheterization showed PVRi 15.5 WU*m2. Marked hypoxemia and PAH persisted despite aggressive therapy with sildenafil, bosentan, intravenous treprostinil, and milrinone. The infant required high doses of inhaled nitric oxide (60 ppm) and manifested significant post-ductal hypoxemia and hemodynamic instability with any attempt at weaning. After discontinuation of sildenafil, initiation, and very slow uptitration of riociguat, the patient was able to maintain hemodynamic stability and wean from nitric oxide over 6 weeks with persistently severe but not worsened pulmonary hypertension. Case 2 is a 4-month-old term male with compound heterozygous SLC25A26 mutation and severe pulmonary hypertension. Initial cardiac catheterization showed PVRi 28.2 WU*m2. After uptitration of sildenafil, bosentan, and IV treprostinil, serial echocardiograms continued to demonstrate near-systemic pulmonary hypertension. He failed multiple attempts to wean off typical doses of iNO (10–20 ppm) over the following weeks with tachypnea, hypoxemia, and worsening pulmonary hypertension on echocardiogram despite continued aggressive combination targeted therapy. After a 24-h sildenafil washout, he was initiated and uptitrated on riociguat with concomitant, successful wean of nitric oxide over one week that was well tolerated. No serious adverse effects in the titration period were observed.

Conclusion: Riociguat may be considered as an adjuvant therapeutic agent in selected children with severe PAH who are poorly responsive to sildenafil therapy and unable to wean from iNO.

KEYWORDS

riociguat, pediatric pulmonary arterial hypertension, pulmonary vasodilator, targeted therapy, pulmonary vasoreactivity, TBX4 mutation, SLC25A26 mutation

Introduction

Pulmonary arterial hypertension (PAH) is associated with poor prognosis and without treatment, can lead to right heart failure and death (1). In recent years, prognosis has improved with the introduction of new PAH - targeted therapies (2, 3). Current approved PAH therapies focus on pulmonary vasodilation and target three different pathways: prostacyclin, endothelin, and nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) pathways (4, 5). However, management of pediatric pulmonary hypertension (PH) remains challenging due in part to the shortage of pediatric-specific clinical trials. Treatment of children is largely based on clinical experience and adult data, and the pediatric use of most PAH targeted therapies is off-label (5).

Riociguat is a drug that acts on the NO-sGC-cGMP pathway which has been approved for use in adults with PAH and chronic thromboembolic pulmonary hypertension (6–8). Unlike phosphodiesterase-5 (PDE5) inhibitors that block the degradation of cGMP, riociguat acts as a direct stimulator of sGC to increase cGMP production in a manner similar to the mechanism for inhaled nitric oxide (iNO). Recent literature supports the efficacy and tolerability of riociguat as an alternative agent for adults with PAH who have insufficient response to treatment with PDE5 inhibitors (7, 9–13). The use of riociguat in pediatric PAH, however, has not been approved because of limited data on its therapeutic use in children (14).

We report the case of two infants with severe suprasystemic PAH who failed to wean from iNO despite combination PH-targeted drug therapy that included sildenafil but were successfully weaned from iNO with the addition of riociguat therapy.

Case reports

Patient 1 is a 6-month-old boy who was born term with a birth weight of 3.3 kg *via* urgent C-section due to maternal bleeding. Prenatal course was otherwise unremarkable. Due to severe hypoxemic respiratory failure at birth, he was treated with intubation, high frequency ventilation, supplemental oxygen (FiO2 = 1.00), iNO, and surfactant administration. Echocardiogram showed right to left ductal shunt consistent with severe PH. Intravenous epoprostenol, sildenafil and milrinone were started in addition to iNO. He underwent cardiac catheterization at 1.5 months of age. Hemodynamic evaluation showed an indexed pulmonary vascular resistance (PVRi) of 15.5 WU*m2 (iNO, oxygen and sildenafil) which decreased to 10.2 WU*m2 with acute uptitration of epoprostenol. Chest CT scan was significant for enlarged pulmonary arteries, patent ductus arteriosus and nonspecific findings suggestive of interstitial lung disease including interlobular septal thickening and ground-glass opacity without pulmonary nodules. He subsequently underwent lung biopsy which demonstrated alveolar simplification with interstitial widening, muscularization of small and medium sized pulmonary arteries and interstitial cells suggestive of pulmonary interstitial glycogenosis but no evidence of alveolar capillary dysplasia. Whole exome sequencing showed a pathogenic 17q23 microdeletion, which encompasses the PH associated TBX4 gene. He was then transferred to our institution at ∼2 months of age for further care. His PAH therapy was titrated to combination therapy with sildenafil, bosentan, intravenous treprostinil, and iNO. His treatment also included an intravenous steroid burst followed by daily inhaled steroids with a modest clinical response but persistent severe pulmonary hypertension by echocardiogram. Over the subsequent 2 months, he continued to manifest hemodynamic instability and post-ductal hypoxemia suggestive of suprasystemic PH. At 4 months of age sildenafil was discontinued due to the lack of a clear clinical response as well as parental concerns regarding the use of this drug. He also developed significant transaminitis prompting cessation of bosentan at 5.5 months of age. He subsequently underwent a second cardiac catheterization at 6 months of age to evaluate his response to ongoing therapy, which showed improvement from his previous catheterization but still severe disease, with a mean pulmonary arterial pressure (mPAP) of 38 mmHg [systemic mean arterial pressure (sMAP) of 49 mmHg], and PVRi of 5.91 WU*m2 (iNO + oxygen + treprostinil). His Qp:Qs improved with increasing doses of iNO and treprostinil (**Figure 1A**). Due to hypotension after the catheterization, his treprostinil dose was maintained at 50 ng/kg/min and iNO increased to 60 ppm delivered *via* noninvasive ventilation. He failed multiple attempts to wean his iNO dose below 60 ppm, as evidenced by right to left ductal shunting on echocardiogram and significant pre- and post-ductal saturation gradients during attempted weans. Because of inability to even slowly wean from this high dose of iNO, the decision was made to start riociguat as additional targeted PAH therapy. Riociguat was initiated at 0.05 mg once daily (0.006 mg/kg/dose), and slowly increased to 0.5 mg/dose thrice daily. He had hypotension without signs of inadequate perfusion after the third dose of riociguat but responded well to saline bolus. Apart from this event, the titration was well tolerated and his hypoxemic events became less frequent. Riociguat was gradually increased to 2 mg/dose TID with iNO weaned and eventually discontinued 7 weeks after riociguat initiation (**Figure 1B**). He had no other reported side effects from riociguat during the titration period. During riociguat uptitration, he was able to wean from noninvasive positive pressure ventilation to nasal cannula. Repeat echocardiogram off iNO showed improved ventricular septal flattening and a

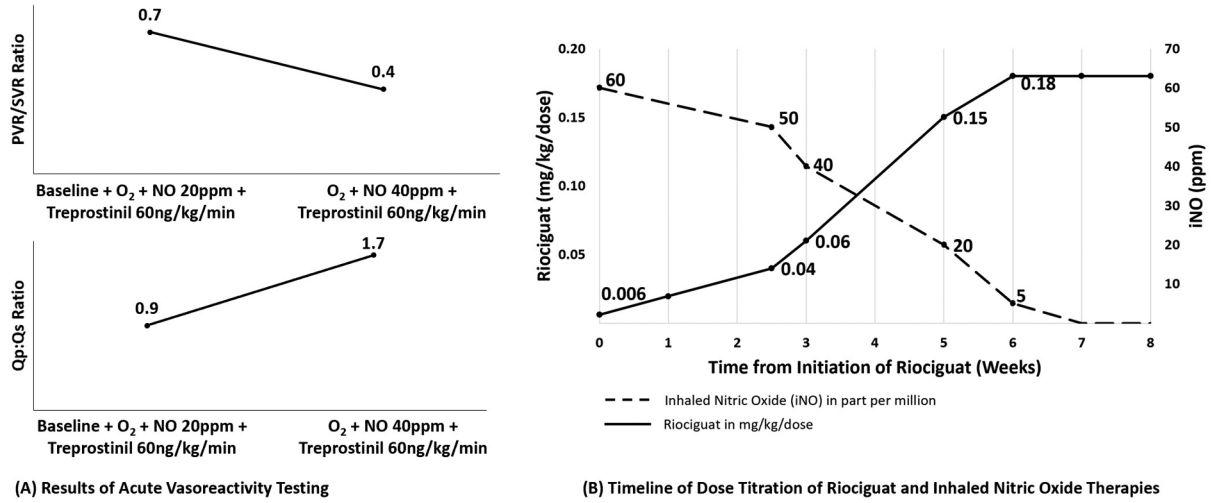

FIGURE 1
Results of acute vasoreactivity testing and timeline of dose titration of riociguat and inhaled nitric oxide therapies for patiennt 1. (A) Results of hemodynamic evaluation for patient 1. With acute increase in nitric oxide dose delivery, we observed (A) decreased pulmonary vascular resistance and (B) increased pulmonary blood flow despite background therapy with sildenafil, treprostinil, high fractional inspired oxygen, and nitric oxide at 20 ppm. (B) Timeline for initiation of riociguat therapy and weaning off inhaled nitric oxide. Riociguat therapy was started at very low dose (0.006 mg/kg/dose = 0.05 mg total dose once per day) and uptitrated slowly over 7 weeks to a dose of 2 mg/dose TID while nitric oxide was weaned over a similar timeframe. Not shown, over the subsequent 6 months his dose was titrated up to final dose of 2.5 mg TID. O_2, oxygen; NO, inhaled nitric oxide; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; Qp, pulmonary flow; Qs, systemic flow.

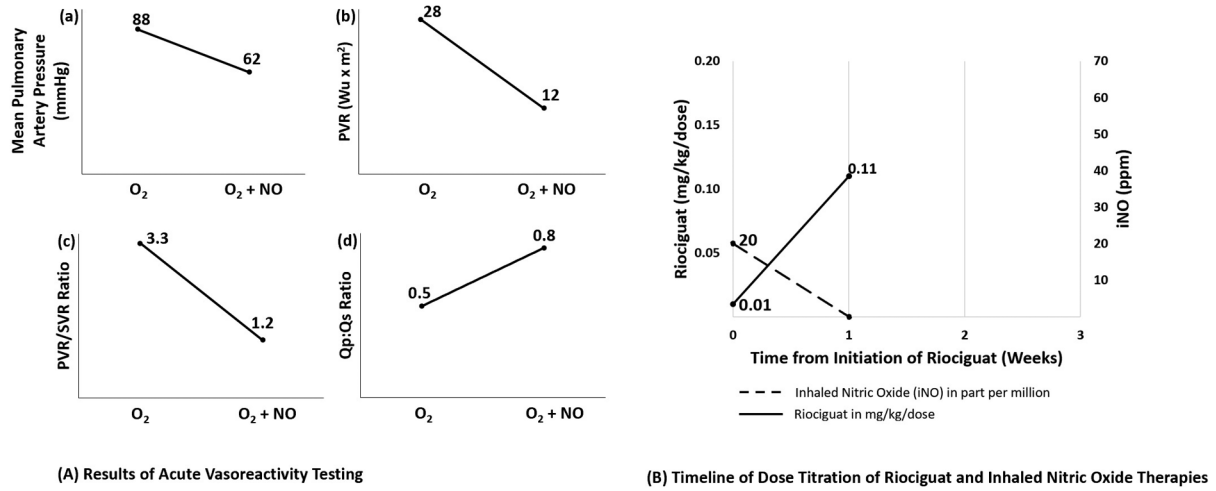

FIGURE 2
Results of acute vasoreactivity testing and timeline of dose titration of riociguat and inhaled nitric oxide therapies for patient 2. (A) Results of acute vasoreactivity testing for patient 2. Acute challenge with increased oxygen (FiO2 1.0) and addition of inhaled nitric oxide at 40 ppm resulted in significant improvement of (A) mean pulmonary artery pressure, (B) indexed pulmonary vascular resistance, (C) PVR:SVR ratio and (D) Qp:Qs ratio. (B) Timeline for initiation of riociguat therapy and weaning off inhaled nitric oxide. Patient 2 was started on riociguat 0.01 mg/kg/dose (0.05 mg total dose three times per day) with a daily dose increase, achieving 0.5 mg/dose TID after 1 week. Nitric oxide was weaned over that same week to off without adverse clinical sequelae noted. Not shown, his dose was titrated up to 2 mg TID over the subsequent four months. O_2, oxygen; NO, inhaled nitric oxide; PVRi, indexed pulmonary vascular resistance; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; Qp, pulmonary flow; Qs, systemic flow.

greater degree of left to right shunting across the PDA, suggesting improved pulmonary vascular resistance. He was discharged home on subcutaneous treprostinil 37 ng/kg/min, riociguat 2 mg TID, and supplemental oxygen. Repeat echocardiogram 2 months later showed continuous low velocity left to right flow in his patent ductus arteriosus, moderate septal flattening and preserved biventricular systolic function. With improved growth and activity level, and no

parental report of intolerance to medications after 4 months on this combination therapy, riociguat was increased to 2.5 mg TID at 13 months of age (body weight 9.4 kg). At latest outpatient follow up, he was 21 months old, World Health Organization functional class II with persistent sub-systemic pulmonary hypertension by echocardiogram, and preserved growth.

Patient 2 is a 4-month-old male born at 38 weeks gestational age. Family history was significant for an 18-month-old sibling with SLC25A26 mutation and severe PAH. Given the family history, he was admitted to the neonatal intensive care unit for observation and was found to have the same compound heterozygous SLC25A26 mutation and severe PAH. He was discharged home during the first week of life with no complications. At 3 weeks of age, he developed tachypnea and poor feeding. Echocardiogram showed moderate septal flattening, moderate right heart dilation and preserved biventricular systolic function. Sildenafil was initiated and he was transferred to our institution. Initial echocardiogram at our institution showed suprasystemic RV systolic pressures and moderate RV dysfunction despite sildenafil therapy. Cardiac catheterization at 7 weeks of age showed mPAP 88 mmHg (sMAP 56 mmHg) and PVRi 28.2 WU*m2 (oxygen), which decreased to mPAP 62 mmHg (sMAP 59 mmHg), and PVRi 12 WU*m2 (iNO + oxygen) (**Figure 2A**). Bosentan, intravenous treprostinil and iNO were added. Despite escalation of PAH therapy with uptitration of intravenous treprostinil to 65 ng/kg/min, he continued to show systemic PH. He also received multiple intravenous steroid bursts with improvement in work of breathing and oxygen requirement but only modest improvement in PAH severity by echocardiogram. He failed multiple attempts to wean off iNO *via* noninvasive ventilation over the following weeks with tachypnea, hypoxemia, and worsening PH on echocardiogram. Due to insufficient response to his combination therapy and inability to wean from iNO, he was started on riociguat at a dose of 0.05 mg TID (0.01 mg/kg/dose) after sildenafil had been held for 48 h. We advanced the riociguat by 0.1 mg/dose daily to initial goal of 0.5 mg/dose TID without evidence of adverse effects. He tolerated a slow wean off iNO and noninvasive ventilation to oxygen supplementation *via* nasal cannula without clinical complications and with improved PAH by echocardiogram over the course of 1 week (**Figure 2B**). Over the following months, riociguat was gradually uptitrated in 0.1 mg/dose intervals to eventual target dose of 2 mg/dose TID. He was able to be discharged home 2 weeks later on riociguat, bosentan, and subcutaneous treprostinil. At 5 months of age, he was re-admitted with Covid-19 pneumonia and had a prolonged hospitalization that included worsening of his PH, uptitration of treprostinil and re-initiation of iNO. At latest follow up, he is 11 months old and managed as an outpatient on supplemental oxygen, riociguat, bosentan, and treprostinil.

Discussion

We report successful transition from sildenafil and iNO to riociguat therapy in two infants with severe PAH who were poorly responsive to sildenafil therapy and had demonstrated difficulty in tolerating even modest weans in iNO therapy (**Figure 3**). To the best of our knowledge, our patients are the youngest in the reported literature to be treated with riociguat. These cases suggest that riociguat merits further investigation for the subset of patients with severe PH who demonstrate need for very high dose iNO to achieve stability or those with clinical sensitivity to withdrawal of iNO, especially in the setting of poor responsiveness to sildenafil therapy.

Given the considerable hemodynamic response to iNO both clinically and during cardiac catheterization, and the clinically observed sensitivity to iNO weans, both infants were started on riociguat with initial dose of 0.05 mg/dose as extrapolated from the case report of the successful treatment of a child with riociguat (14). In both cases, riociguat was prescribed using the clinical judgement of the treating team, not within the context of a clinical trial. Recognizing the limited data and uncertain risk of riociguat use in children, we utilized shared decision making in choosing to initiate and titrate the riociguat. It is important to note that riociguat must not be used in combination with PDE5 inhibitors because of the risk of severe systemic arterial hypotension (15). In addition, riociguat should be avoided in those with hepatic or renal impairment (16, 17). In both our patients, sildenafil was discontinued for at least 48 h before riociguat therapy was initiated. Patient 1 had transaminitis (ALT 3.4x elevated, AST 1.2x elevated) but normal synthetic liver function. His transaminitis improved ~6 months after discontinuing bosentan. Both our patients had normal renal function. No clinical worsening occurred during the sildenafil-free period. Both tolerated slow riociguat advance with iNO gradually weaned to prevent rebound pulmonary hypertension (18–21).

Our approach to these patients is supported by the experience in adult PAH. Recent literature reports clinical efficacy of transitioning PDE5 inhibitors to riociguat for those who do not reach treatment goals. The pivotal study PATENT-1 is a double-blind randomized placebo-controlled trial of PAH patients. In this study, patients who were treated with riociguat had improvement in 6-minute walk distance (6MWD), pulmonary vascular resistance (PVR), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), World Health Organization functional class (WHO-FC), time to clinical worsening, and Borg dyspnea scale rating (7). These improvements were sustained in the long term extension study PATENT-2 (12, 13). Similar findings were observed in the RESPITE study (9). RESPITE is an open label study that investigated the benefits of switching from stable doses of sildenafil or tadalafil to riociguat in PAH patients who remain

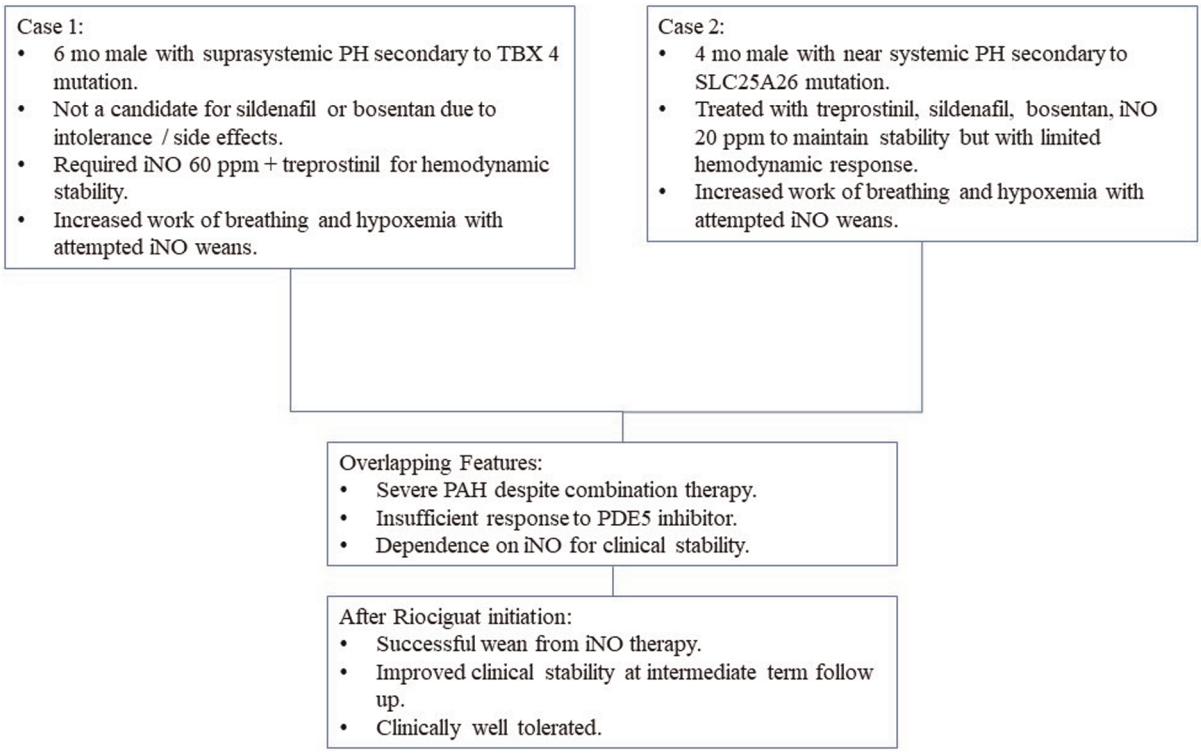

FIGURE 3
Summary of clinical cases.

symptomatic and have insufficient response to PDE5 inhibitors. At the end of the study period, improvements were seen in the 6MWD, NT-proBNP, WHO-FC and hemodynamic parameters. However, despite these studies that report improved treatment efficacy after switching from PDE5 inhibitors to riociguat in adults, there is very limited data or experience with use of riociguat in children (22–24).

The clinically observed greater efficacy with riociguat compared to sildenafil in our patients may be explained by its dual mode of action on sGC. Since riociguat works by both increasing the sensitivity of sGC to endogenous NO by stabilizing NO-sGC binding, and directly stimulating sGC independent of NO (25), the effect of riociguat may be greater in certain PAH patients who have a defective NO-sGC-cGMP pathway leading to insufficient or non-sustained response to PDE5 inhibitors (26–33). In addition, it has been shown that other phosphodiesterases could degrade cGMP in the presence of PDE5 inhibition, causing PDE5 inhibitors to be less effective (34).

Several preclinical studies provide evidence of mechanisms by which riociguat could be preferable to sildenafil in certain PAH populations. The efficacy of riociguat and sildenafil in the setting of hypoxia, was compared in studies involving rat and human pulmonary arteries (35). While both riociguat and sildenafil inhibited hypoxic pulmonary vasoconstriction, riociguat was found to be more effective as vasodilator than sildenafil with near maximal relaxation compared to ~50% relaxation with sildenafil. Moreover, riociguat was 3-fold more potent under hypoxic conditions and did not worsen ventilation-perfusion coupling. The authors hypothesized that the observed difference was due to low basal NO activity leading to insufficient cGMP despite strong PDE5 inhibition. Alternatively, riociguat may also be more effective under chronic states of hyperoxia. Studies have shown that exposure of neonatal lungs to supraphysiologic oxygen levels may induce cellular dysfunction that can persist beyond the neonatal period (35–39), and even brief exposure to hyperoxia can lead to inactivation of endothelial NO synthase (eNOS), decreased sGC responsiveness to NO, increased PDE5 activity, and induction of mitochondrial reactive oxygen species which directly increase PDE5 activity (33, 35–37). In addition, exposure of neonatal lungs to oxidative stress affects the NO-sGC-cGMP pathway through oxidation of the heme-bound sGC (39–42). The decreased responsiveness of sGC to NO in such states may lead to lower levels of cGMP. In this scenario, riociguat could be superior to sildenafil by directly stimulating sGC, thereby increasing cGMP generation rather than decreasing breakdown through PDE5 inhibition (39). Similarly, increased cGMP levels after oxidative stress and greater pulmonary vasodilation compared to oxygen, iNO,

acetylcholine or sildenafil were observed in earlier studies of the sGC activator cinaciguat in ovine models of pulmonary hypertension (41–43). These provide more evidence of the effectiveness of sGC modulators in conditions of oxidative stress leading to increased concentrations of NO-insensitive sGC and low cGMP levels.

In addition to the vasodilatory effects of riociguat noted in these studies, several pre-clinical studies have also shown antiproliferative, antifibrotic, and anti-inflammatory effects of riociguat and other sGC stimulators (26, 44–49) such that riociguat may have beneficial effects on multiple pathologic mechanisms contributing to PH. A study involving neonatal rats suggested that riociguat may prevent hyperoxia-induced lung injury with decrease in lung inflammation, improvement of both lung alveolar and vascular development, and decrease in vascular remodeling (46). Stimulation of soluble guanylate cyclase also reversed RV hypertrophy (RVH) and pulmonary vascular remodeling in mice models (26, 45). In another study using bleomycin-exposed mice, riociguat, compared to sildenafil, significantly improved pulmonary fibrosis and pulmonary inflammation in addition to its effect on PH and RVH (47). Similarly, riociguat significantly decreased RVH, increased cardiac output, and decreased total PVR compared with sildenafil in rats with severe PAH induced by hypoxia and the vascular endothelial growth factor receptor antagonist SU5416 (48). Compared with sildenafil, the effects of riociguat on RV function, and the neointima/media ratio of pulmonary arteries were significantly better. Furthermore, riociguat was shown to prevent the development of PH, RVH and vascular remodeling, as well as reduce inflammatory cell infiltrate and apoptosis of alveolar and endothelial cells in the lungs compared with controls in mouse model of chronic obstructive pulmonary disease and PH (49). These secondary effects may lead to improvement of cardiac hemodynamics and lung function, and therefore, pulmonary hypertension. There is also increasing evidence that maladaptation of the inflammatory and immune systems contribute to pulmonary vascular remodeling and PH such that therapies that directly modulate inflammatory processes have become a recent focus of clinical studies in PAH (50, 51). Both our patients received systemic and inhaled steroids at various times with improvement in work of breathing and oxygen requirement but only modest improvement in PAH severity. From this mixed clinical observation, it is difficult to say what, if any, role pulmonary inflammation played in each patient's clinical course, but this is an important area for future study generally in PAH and specifically in the utility of riociguat.

Lastly, riociguat may have the additional benefit of eliminating the potential direct interaction between bosentan and sildenafil (52), thus improving the therapeutic plasma concentrations and efficacy of both medications.

Overall, riociguat has been well tolerated in adult clinical studies. The most commonly reported drug-related adverse events in ~40–50% of the patients include hypotension, syncope, dyspepsia, nausea, vomiting, dizziness, headache, cough and upper respiratory infections (7, 9, 10, 12, 13). Adverse events leading to discontinuation of riociguat were reported in 3%–9% of patients (7, 9, 10, 53). Although most of the adverse events were not considered serious, there were cases of significant hemoptysis and pulmonary hemorrhage seen in these studies (7, 9, 12). In our experience, Patient 1 had borderline hypotension without signs of inadequate end organ perfusion during the initiation period of riociguat that resolved after a single 10 cc/kg saline bolus. No other adverse effects in the titration period or follow up were observed in either case, which is similar to the report by Spreeman (14). Although our patients are too young to describe symptoms, there was no increase in fussiness, changes in activity or worsening feeding intolerance noted that may indicate these reported drug-related adverse events. Additionally, a previous study demonstrated dose-related adverse effects of sGC agonists on long bone growth including bone resorption and variable bone formation (54). Due to the reported multifocal bone changes in rats given riociguat, Patient 1 had serial hand radiographs which did not reveal any bone changes. This is consistent with the study in neonatal rats treated with riociguat which showed no effects on bone growth or structure (46). PATENT-CHILD, an open label study designed to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of riociguat in children with PAH aged 6–17 years old, is currently ongoing and may provide additional support on the use of riociguat in pediatric PAH (NCT02562235) (55).

Our study has several limitations. First, this is an observational study of only two patients with intermediate duration of follow up and so we are unable to evaluate efficacy and safety of long-term therapy with riociguat. We also cannot identify characteristics or risk factors of patients who may have a more favorable response to early treatment with riociguat instead of a PDE5 inhibitor. Since both our patients have heritable PAH, the pattern of their genetic variants may have influenced their response to PDE5 inhibitor and riociguat therapies. Future precision-medicine studies of how patients with different subtypes of group 1 PAH respond to different targeted therapies will be important (56, 57). Our reported outcomes are also limited to clinical and echocardiographic data without repeat hemodynamic data. Since this is performed at an altitude of 1,600 meters, the hemodynamic measurements and the observed response of our patients to both riociguat and PDE5 inhibitor may also vary at different elevations. Additionally, our approach to initial dosing and titration evolved based on our previous experience and individual patient response, and may not be applicable to the entire pediatric population. An in-depth discussion of the mechanisms of action and dosing of all PAH therapies used in these patients is beyond the scope of our report. Finally, although we did not see any adverse

events after stopping sildenafil prior to initiating riociguat, interruption of this therapy remains a major concern especially in critically-ill patients. Future studies are necessary to determine the optimal dosing, drug-free and dose adjustment periods for riociguat in children.

Conclusion

Our report suggests that riociguat may be considered as an adjuvant therapeutic agent in selected children with severe PAH who are poorly responsive to sildenafil and unable to wean from iNO therapy. Further studies are needed to better define criteria for determining the efficacy and safety of riociguat use in young children, and to determine the subset of patients who will benefit from early therapy with riociguat instead of PDE5 inhibitors.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LD: writing original draft, review and editing (equal); DDI: review and editing (equal). SA: review and editing (equal). AG: review and editing (equal). JM: review and editing (equal). JB: review and editing (equal). KM: review and editing (equal). BF: conceptualization, review and editing (equal). All authors contributed to the article and approved the submitted version.

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Conflict of interest

The University of Colorado contracts with Actelion, Bayer, Gilead, GSK, Janssen, Lilly, and United Therapeutics for D. Dunbar Ivy, MD to be a consultant and perform clinical trials. Steve Abman, MD serves in the Data Safety Monitoring Board for Bayer Pharmaceuticals. The other authors declare that there is no conflict of interests.

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EDITED BY
Angela Bates,
University of Alberta, Canada

REVIEWED BY
Paul Critser,
Cincinnati Children's Hospital Medical Center, United States
Brian Mendel,
National Cardiovascular Center Harapan Kita, Indonesia

*CORRESPONDENCE
Georg Hansmann
georg.hansmann@gmail.com

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Case report: Rescue treatment with add-on selexipag in a preterm infant with suprasystemic pulmonary hypertension, pulmonary capillary hemangiomatosis, and isolated pulmonary vein stenosis

Hosan Hasan[1,2], Klea Hysko[1,2], Thomas Jack[1,2], Jens Dingemann[3], Martin Wetzke[4] and Georg Hansmann[1,2]*

[1]Department of Pediatric Cardiology and Critical Care, Hannover Medical School, Hannover, Germany, [2]European Pediatric Pulmonary Vascular Disease Network, Berlin, Germany, [3]Department of Pediatric Surgery, Hannover Medical School, Hannover, Germany, [4]Department of Pediatric Pulmonology, Hannover Medical School, Hannover, Germany

An extremely dystrophic, premature female infant, born at 25 3/7 weeks of gestational age (birth weight: 430 g) with severe pulmonary hypertension (PH), was admitted to our neonatal intensive care unit (ICU) requiring cardiorespiratory support, including mechanical ventilation and pulmonary vasodilators such as inhaled nitric oxide (iNO) and continuous intravenous sildenafil infusions. The diagnosis of bronchopulmonary dysplasia (BPD) was made. A hemodynamically relevant, persistent ductus arteriosus (PDA) was surgically ligated after failed pharmacologic PDA closure using indomethacin and ibuprofen. The patient was discharged with an estimated 2/3 systemic pulmonary artery pressure. One month after hospital discharge, on low-flow oxygen supplementation (0.5 L/min FiO2 100%), at the corrected age of 16 weeks, she was readmitted to our emergency department with signs of respiratory distress and circulatory decompensation. Echocardiography demonstrated suprasystemic PH. Severe PH persisted despite initiated invasive mechanical ventilation, triple vasodilating therapy [iNO, macitentan, and continuous intravenous (IV) sildenafil], as well as levosimendan, milrinone, and norepinephrine for recompensation from cardiac shock. Thus, we started off-label oral selexipag therapy (oral IP receptor agonist) in the smallest patient reported so far (4 kg body weight). Subsequently, RV systolic pressure decreased to half-systemic, allowing successful weaning of iNO, norepinephrine, and milrinone, and extubation of the patient over 4 days. The infant was discharged 4 weeks after pediatric intensive care unit (PICU) admission in stable cardiorespiratory condition, with an oral, specific, triple antihypertensive PAH-targeted therapy using selexipag, macitentan, and sildenafil as well as oxygen therapy at low-flow (0.5 l/min) and spironolactone.

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The first cardiac catheterization at the age of 9 months under aforementioned triple PAH-targeted therapy revealed mild PH with 35% systemic PA pressure (mPAP/mSAP = 0.35) and isolated pulmonary vein stenosis. A transthoracic biopsy at the age of 12 months confirmed the diagnosis of BPD and further showed pulmonary interstitial glycogenosis and severe pulmonary capillary hemangiomatosis, without involvement of the pulmonary venules (chILD A2, A3, and B4 according to the Deutsch-Classification). The patient is currently in stable cardiorespiratory condition undergoing triple PH-targeted therapy including selexipag. This report highlights the potential benefits of the oral prostacyclin mimetic selexipag as an early add-on PH-targeted drug in chronic PH of infancy (cPHi).

KEYWORDS

bronchopulmonary dysplasia (BPD), pulmonary hypertension (PH), neonatology, selexipag, prematurity, intensive care

Introduction

Bronchopulmonary dysplasia (BPD) is a condition with impaired respiratory function of the newborn, that primarily affects preterm infants, defined as the need for respiratory support (high-flow-nasal cannula, continuous positive airway pressure, mechanical ventilation) even in the absence of supplemental oxygen at corrected age of 36 weeks (1). The imbalance between lung-injury and -repair processes in developing, still immature lungs, alveolar simplification, and the arrest of vascular growth are key determinants in the pathophysiology of BPD (2–5). Frequently, BPD is associated with pulmonary hypertension (PH) (6–8). Indeed, in the context of BPD, disturbance of alveolar diffusion, abnormal vascular remodeling as well as the rarefication of pulmonary vessels (growth-arrest) lead to an increasing pulmonary vascular resistance (PVR) with subsequent RV failure (6, 7). About 25% of infants with moderate to severe BPD develop secondary PH (Group 1.6/3.5 PH) (9). About 31–47% of preterm infants die within 2 years after diagnosis of BPD-associated PH (BPD-PH) (10, 11). In particular, extremely premature infants born at 23–25 weeks of gestation are at substantial risk for PH (12). Beyond the substantial mortality, BPD-PH is also associated with impaired body growth, neurodevelopmental disorders, high oxygen demand, feeding problems, and a higher hospitalization rate than isolated BPD (13).

Advanced pharmacotherapy for pediatric PH undergoes rapid development today. Currently, many drugs with different routes of administration and targeted pathways are used to reduce PVR and consequently pressure overload on the RV, mainly by pulmonary vasodilatation (and anti-inflammation, anti-proliferation): phosphodiesterase-5 (PDE5) inhibitors (sildenafil), endothelin-receptor-antagonists (ERA) (macitentan, bosentan), soluble guanylate cyclase (sGC) stimulators (riociguat), prostacyclin agonists/analogues/mimetics (treprostinil, iloprost, epoprostenol, selexipag) (8). The majority of aformentioned PAH-targeted drugs, including selexipag are currently used off-label in children with PH in expert centers (14). Selexipag is the first orally administered selective prostacyclin receptor (IP) agonist that has been shown to induce vasodilation and to inhibit pulmonary (peri)vascular inflammation and –proliferation. Although our recently published multicenter study on add-on selexipag treatment in severe pediatric PH (15) highlighted the safety and efficancy of the drug, its use in preterm infants with PH has not been investigated so far. The following case report focuses on the evaluation and discussion of selexipag treatment in a preterm infant with chronic PH of infancy (cPHi) (6) and demonstrates the diagnostic work up needed in complex BPD-PH.

Case report

Baseline patient characteristics

The affected female preterm infant was born at 25 3/7 weeks postmenstrual gestational age, weighing 430 g [small for gestational age (SGA)]. Preterm birth due to maternal eclampsia and pathologic cardiotocography (CTG), lead to delivery by primary cesarean section. The postnatal chest x-ray (CXR) in our neonatal intensive care unit (NICU) showed acute respiratory distress syndrome (ARDS) grade 2–3 that required endotracheal intubation and mechanical ventilation. On the second day of life, echocardiography (Echo) showed severe persistent pulmonary hypertension in the newborn (PPHN). Thus, we initiated inhaled nitric oxide

(iNO), muscle relaxation and continuous intravenous sildenafil-infusion. Intravenous (IV) dexamethason was applied at the age of 3 weeks. Subsequently the infant could be extubated, followed by continuous positive airway pressure support (CPAP). A hemodynamically significant patent ductus arteriosus (PDA) (16) was initially treated with ibuprofen and indomethacin, but ultimately closed by surgical ligation at 7 weeks of postnatal age. The postoperative Echo revealed tricuspid regurgitation (TR) grade 1 with an estimated RV systolic pressure (RVSP) of 3/4 systemic pressure and qualitatively sufficient biventricular systolic function. At 36 weeks of corrected gestational age, the patient was under CPAP respiratory support with 15 L/min flow and FiO2 of 80%, thus severe BPD according to the classification of BPD severity [Brumbaugh (19)] was present. CPAP was weaned and exchanged against low-flow oxygen supplementation with 1 L/min 100% O2 at 16 weeks of life-age (corrected age of 3 weeks). At the corrected age of 10 and 14 weeks, transthoracic echocardiography showed no TR, moderate dilation of the right atrium (RA), and an estimated half systemic RVSP. We discharged the infant in the 20th week of postnatal life, at the corrected age of 7 weeks and a body weight of 3650 g (10th percentile). At the time of discharge, she had not received any specific PH-targeted medication besides low flow supplemental oxygen since the PDA ligation.

Acute decompensation in PH-bronchopulmonary dysplasia

In the 24th week of life, 4 weeks after NICU discharge, the patient presented in decreased general condition with cardio-pulmonary decompensation at our emergency department, with tachypnea, dyspnea, paleness, and lethargy. Laboratory tests revealed global respiratory failure with hypoxia (SpO_2 80%) and hypercapnia (pCO_2 106 mmHg), acidosis (pH 7.09, lactate 7.2 mmol/L, base deficit -3.2 mmol/L), as well as greatly increased cTroponin T (149 ng/L) and NT-proBNP (> 35.000 ng/L). Mean systemic blood pressure was low [mean systemic arterial pressure (mSAP) 25 mmHg] and central venous pressure high, so that we assumed severe PH crisis. A few days before the acute decompensation, the patient presented at our emergency department due to drops in oxygen saturation down to 50% in the patient's domestic monitoring system and a mild infection of the upper respiratory tract. However, the patient was not admitted to our hospital due to stable cardiorespiratory status and normal oxygen saturation at presentation. No echocardiography was performed at first presentation. After immediate admission to our pediatric intensive care unit (PICU), the first Echo showed TR grade I with estimated suprasystemic RVSP (RVSP 81 mmHg + right atrial v wave, with systolic SAP of 63 mmHg), moderate to severe systolic RV dysfunction, and severe RV hypertrophy [increased right ventricular anterior wall thickness (RVAW) of 6 mm]. After primary intraosseous vascular access and endotracheal intubation, mechanical ventilation with iNO and oxygen supplementation was initiated. After placement of a central venous catheter, continuous infusions of sildenafil, epinephrine, and milrinone were established.

On day 2 in PICU, transthoracic Echo still showed severe PH with an estimated RVSP of systemic arterial pressure level with a moderately dilated RV and moderate RV systolic dysfunction (**Figures 1A,B**). The pulmonary artery (PA) was much larger in caliber than the ascending aorta. The left ventricle (LV) appeared underfilled but had normal systolic function. Systemic arterial pressure was 76/46 (mean 61) mmHg. We consequently exchanged epinephrine for norepinephrine, started the ERA macitentan *per os*, transfused packed red blood cells (PRBC) (goal Hb 12–14 g/dl) and started levosimendan infusion the next day over a course of 24 h. Oral Spironolactone (5 mg twice daily) was added to the treatment regime on PICU day 1 (see **Table 1** for all pertinent medications used during the PICU course). On day 4 in the PICU, 2 days after starting macitentan (dual PAH-targeted therapy), NTproBNP had decreased to 2.000 ng/L and Troponin T to 57 ng/L. Nevertheless, the patient remained dependent on intensive care including muscle relaxation, mechanical ventilation, iNO, additional oxygen, and continuous sildenafil infusion. Two attempts of weaning off both muscle relaxation and iNO ended up in severe, life threatening PH crisis, so that weaning mechanical ventilation was impossible.

Add-on selexipag as pulmonary hypertension rescue therapy

Subsequently, on day 4 in the PICU, we initiated add-on off-label Selexipag treatment with a starting dose of 50 µg 0–0–1, increased to 50 µg twice daily (1–0–1) the next day and then gradually increased the dose by 50 µg daily (first 2 days), and then by 100 µg daily to a final dose of 400 µg/12 h. Technically, the 200 or 400 µg selexipag tablet was dissolved in 10 ml water and the according dose was administrated *via* the nasogastric tube. The cardiorespiratory condition then improved quickly: We stopped muscle relaxation (*cis*-atracurium) and started weaning iNO on PICU day 5, slowly weaned off iNO and norepinephrine at PICU day 6 and 7, and ultimately extubated the patient against high flow and weaned off milrinone on PICU day 8. Lastly, we were able to transfer the patient to the intermediate care unit (IMC) under tripple PH targeted therapy (sildenafil, macitentan, selexipag) 9 days after PICU admission (**Table 1**).

Further in the clinical course, the patient required intravenous broad-spectrum antibiotics (meropenem and vancomycin) over a span of 14 days, due to central venous line (CVL) associated sepsis, without the necessity for new

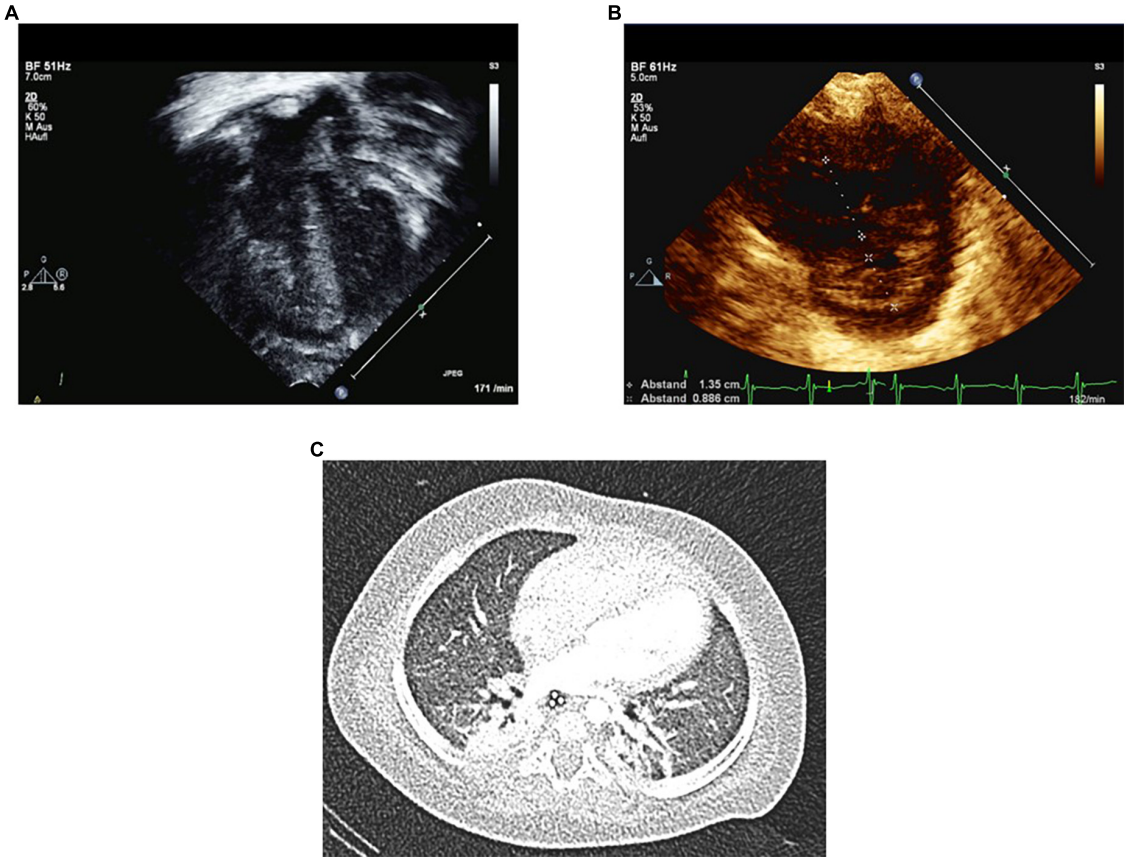

FIGURE 1
Echocardiography on day 2 and Chest CT on day 7 in PICU at the age of 6 months. Several Echo variables and ratios indicate severe PH on the second PICU day in acute cardiorespiratory decompensation. Panel **(A)** shows severe RV hypertrophy and RV dilation. Panel **(B)** shows increased RV/LV end-systolic diameter ratio of 1.5. Panel **(C)** shows chest CT with atelectasis of the right upper lobe and mild mosaic perfusion. No signs of cysts or bullae were identified.

intensive medical treatment. On day 33 after PICU admission (08/25/2020), discharge from the hospital was feasible at a body weight of 5 kg and tripple antihypertensive PAH-targeted medication (sildenafil 4 mg q 6 h; macitentan 4 mg once daily, selexipag 400 µg q 12 h) as well as low flow oxygen supplementation (0,5 L/min 100% O2).

Diagnostic work up

Chest computed tomography

The patient underwent a chest-computed tomography (CT) already on day 9 in the PICU at the age of 6 months, in order to evaluate the pulmonary parenchyma and vessels (**Figure 1C**). CT images showed hypoplasia of lung parenchyma with alveolar simplification and diffuse mosaic perfusion, typically associated with extreme premature birth. No cysts or bullae were identified. Additionally, we found an atelectasis of the right upper lobe, which was bronchoscopically flushed out during the same inpatient stay.

Right-left-heart-catheterization

A total of 3 months after PICU discharge and initiation of triple combination antihypertensive PH-targeted drug therapy, we performed right-left heart catheterization (RLHC) (**Figure 2**) at the age of 9 months. RLHC is essential for an accurate diagnosis of PH (8, 17, 18) and for new findings regarding relevant primary or secondary pathologies. Pressures derived from RLHC were as follows (mmHg): mean right atrial pressure (mRAP): 6; RV systolic/diastolic pressure: 34/6; pulmonary arterial pressure (PAP) systolic/diastolic: 29/17; mean PAP (mPAP): 23; systemic arterial pressure (SAP) systolic/diastolic: 76/47; mean SAP (mSAP): 61; pulmonary artery wedge pressure (PAWP): 10–12. The mPAP/mSAP ratio was 0.38, i.e., below half systemic PA pressure, and strongly dropped compared to PICU admission 3 months earlier (supra systemic RVSP). Pulmonary vascular resistance (PVR: 4.1 WU•m^2) was moderately elevated. PVR/SVR ratio was 0.26. Considering Cardiac Index (Qsi: 3.55 l/min/m^2), the Qp/Qs ratio was 0.9. According to the 6th-World Symposium on PH (WSPH)–hemodynamic definition of

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TABLE 1 Medications used in PICU for infant (body weight 4.3 kg) with acute cardiorespiratory decompensation and PH crises.

Oral PH-targeted medication	Starting dose	Increase per dose	Final dose/day	PICU day	Comment
Sildenafil (four times daily)	1 mg per dose	1 mg	4 × 4 mg	1	Increase in CI. Decrease in PVR. Maintenance dose: 0.5–1 mg/kg/dose three (> 1 year old) or four times (< 1 year old) daily PO. In this case: transitioning from IV sildenafil.
Macitentan (once daily)	2 mg per dose	1 mg	1 × 4 mg	2	Increase in CI. Decrease in PVR. Not recommended in patients with moderate or severe hepatic impairment.
Selexipag (twice daily)	50 μg per dose	50–100 μg (see text)	2 × 400 μg	4	Prostacyclin IP receptor agonist. Reduction of morbidity/mortality event in adult PAH.
Intravenous medication					
Epinephrine	0.02 μg/kg/min	–	0.02 μg/kg/min	1–2	Positive inotrope. Increases myocardial oxygen consumption, tachycardia.
Norepinephrine	0.2 μg/kg/min	–	0.2 μg/kg/min	2–7	Increases SVR and PVR.
Sildenafil	3.1 mg/kg/day	–	3.1 mg/kg/day	2–9	Sildenafil 1–4 mg/kg/day, depending on systemic blood pressure.
Milrinone	0.7 μg/kg/min	–	0.7 μg/kg/min	2–8	Lowers PVR. Caution: systemic arterial hypotension.
Levosimendan	0.12 μg/kg/min	–	0.12 μg/kg/min	3	Lowers PVR. Caution: systemic arterial hypotension. Long half-life.
Morphine	0.18 mg/kg/h	–	0.18 mg/kg/h	2–9	Slowly weaned off during PICU stay.
Midazolam	0.09 mg/kg/h	–	0.09 mg/kg/h	2–9	Slowly weaned off during PICU stay.
Cis-atracurium	0.32 mg/kg/h	–	0.32 mg/kg/h	2–4	During mechanical ventilation.
Rocuronium	1 mg/kg/dose	–	1 mg/kg/dose	4–5	Single dosing. In this case: transitioning from *cis*-atracurium.
Inhaled medication					
Nitric oxide	20 ppm	–	20 ppm	2–6	Monitor Met-Hemoglobin. Selective fall in PVR. Rebound PH on weaning off iNO (risk can be reduced by concomitant use of sildenafil).

All medications that we administered in PICU with effects on hemodynamics, are listed. Total stay on PICU were 9 days. Comments are from the EPPVDN consensus statement on the treatment of pediatric pulmonary hypertension, please refer for detailed information (DOI: 10.1016/j.healun.2019.06.02).

PH (19), all criteria of isolated precapillary PH were fulfilled. Under the condition of 30 ppm iNO and 100% Oxygen, the acute vasoreactivity test (AVT) was negative as defined by the EPPVDN (i.e., neither a decrease of the mPAP nor of the PVR/SVR ratio by at least 20%) (8). Furthermore, by angiography, we could identify an isolated pulmonary vein stenosis (PVS) at the orifice of the left upper pulmonary vein (LUPV) in the left atrium (LA), with a LUPV pressure of 22 mmHg, mean LA pressure of 10 mmHg, and thus a pressure gradient dP mean LUPV to LA of 12 mmHg. The other three pulmonary veins were not obstructed, so we did not consider further intervention necessary at this stage.

Lung biopsy

Lung biopsy is an invasive diagnostic method for the classification of diffuse parenchymal lung disease (DPLD) or so-called children's interstitial lung disease (chILD). Before lung biopsy, and solely based on the medical history and non-invasive diagnostics, the patient was classified as group A2 (DPLD-Growth abnormalities deficient alveolarization) and group B4 (DPLD-related to lung vessels structural processes) according to the Deutsch-Classification (20, 21). We performed lung biopsy due to recurring severe respiratory infections, treated with multiple steroid pulses with moderate effects. Lung biopsy was performed by pediatric surgeons through a posterolateral mini-thoracotomy under general anesthesia without any complications, at the corrected age of 9 months. Histology confirmed BPD with hypoalveolarisation and an abnormal structure of the pulmonary vasculature with smooth muscle cell proliferation and altered extracellular matrix. A major histological finding was a variable pulmonary capillary hemangiomatosis (PCH), showing proliferating capillaries in row and grape-like formations around the alveolar septal tissue, that partly infiltrated alveolar septal tissue resulting in septal thickening. No participation or alteration of the pulmonary veins, particularly no obliterative fibrosis of the post-capillary venules was found. Small areas of the biopsy showed mild pulmonary interstitial glycogenosis (PIG) with cytoplasmic accumulation of glycogen in the interstitial cells (**Figure 3**).

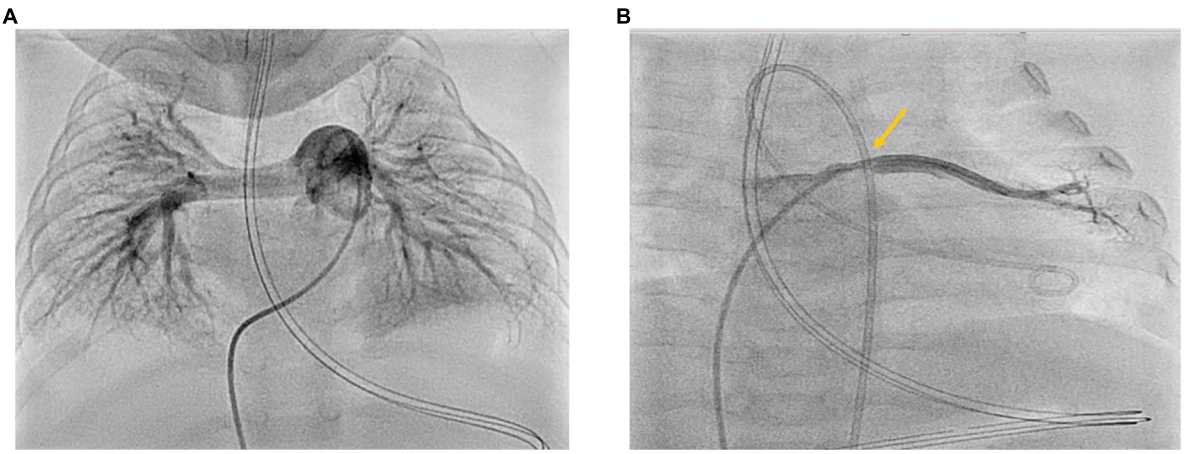

FIGURE 2
(A,B) Cardiac catheterization 3 months after PICU discharge at the age of 9 months. Right-Left heart catheterization 3 months after acute cardiorespiratory decompensation and initiation of triple oral PH-targeted medication (Sildenafil, Macitentan, Selexipag). Panel **(A)** shows angiography of the dilated proximal pulmonary artery: PVRi 4.1 WU•m^2; mPAP 23 mmHg; mSAP 48 mmHg; mPAP/mSAP 0.48 (<half systemic PAP). Panel **(B)** shows angiography of the left upper pulmonary vein with the stenosis at entry to LA with LUPV pressure of 21–22 mmHg and dP mean LUPV to LA of 12 mmHg.

Genetic testing

Gentic testing by means of whole exom sequencing (WES) revealed a heterozygous mutation in the Endoglin (ENG) gene (c.172_1728del; p.{lle575del}) in the infant and the mother as a variant of unknown significance (VUS). There was no other pathogenic mutation in the following potential disease-causing genes (PH- and ILD-Panel): ABCA3, CSF2RW, FLNA, FOXF1, SFTPB, SFTPC, TBX4, ACVRL1, BMPR2, CAV1, EIF2AK4, GDF, KCNA5, KCNK3, SMAD4, SMAD9, AGPAT2, ALMS1, BSCL2, FOS, PPARG.

Follow-up and outcomes

In the further course, several upper respiratory tract infections (URTI) (5–6×/year) lead to exacerbations of cardiorespiratory condition, that frequently required high flow oxygen and antibiotic treatment. The patient regularly responded well to systemic steroid pulse therapy in severe respiratory exacerbations (10–20 mg/kg/day methylprednisolon on 3 consecutive days).

Currently, feeding difficulties and slow growth are still present: The patient is still completely dependent on high calorie tube feeding through a percutaneous endoscopic gastrostomy (PEG) tube due to dysphagia and the inability of oral feeding. The patient is currently living with her family at home, supported by a pediatric nurse for outpatient care; she receives regular training for dysphagia and neurodevelopmental disorder. Follow-up visitis are conducted at a regular interval of 3 months in specialized pediatric cardiology and pulmonology clinics. Under a triple antihypertensive PAH-targeted medication (sildenafil, macitentan, selexipag), spironolactone, and low flow oxygen supplementation, the last Echo in April 2022 did not show any evidence for severe or higher grade PH. The patient had significant catch-up growth and is in very good general condition, with slow but steady motoric and mental development. At the current age of 2 years and 4 months, she crawls, pulls herself up on objects and is able to sing songs more and more understandably.

Discussion

Generally, BPD is a heterogeneous condition with a variable degree of respiratory dysfunction, whose subtypes are hardly defined. BPD-PH due to pulmonary vascular disease (PVD) is characterized by alveolar simplification, impaired pulmonary angiogenesis, vascular inflammation, and obliterative pulmonary vascular remodeling, leading to respiratory failure and increasing PVR with consecutive RV-failure (6, 7). Within the classification of PH, BPD-PH is assigned to group 3: PH associated with lung disease (8). About 25–40% of infants affected by BPD, develop secondary chronic PH (22), a condition with a significantly higher mortality rate than in isolated BPD (10, 23).

We recently coined the term *"chronic PH of infancy (cPHi)"* (6) that applies to the infant described in this current case report. Besides developmental lung diseases including BPD, other conditions such as congenital cardiovascular disease with increased pulmonary blood flow, e.g., left-to-right shunting *via* a large PDA or VSD, frequently lead to elevated PVR and chronic PAH, if not treated in a timely fashion (approx. 4–8 months of age) (16). Depending on the degree of left to right shunting and related

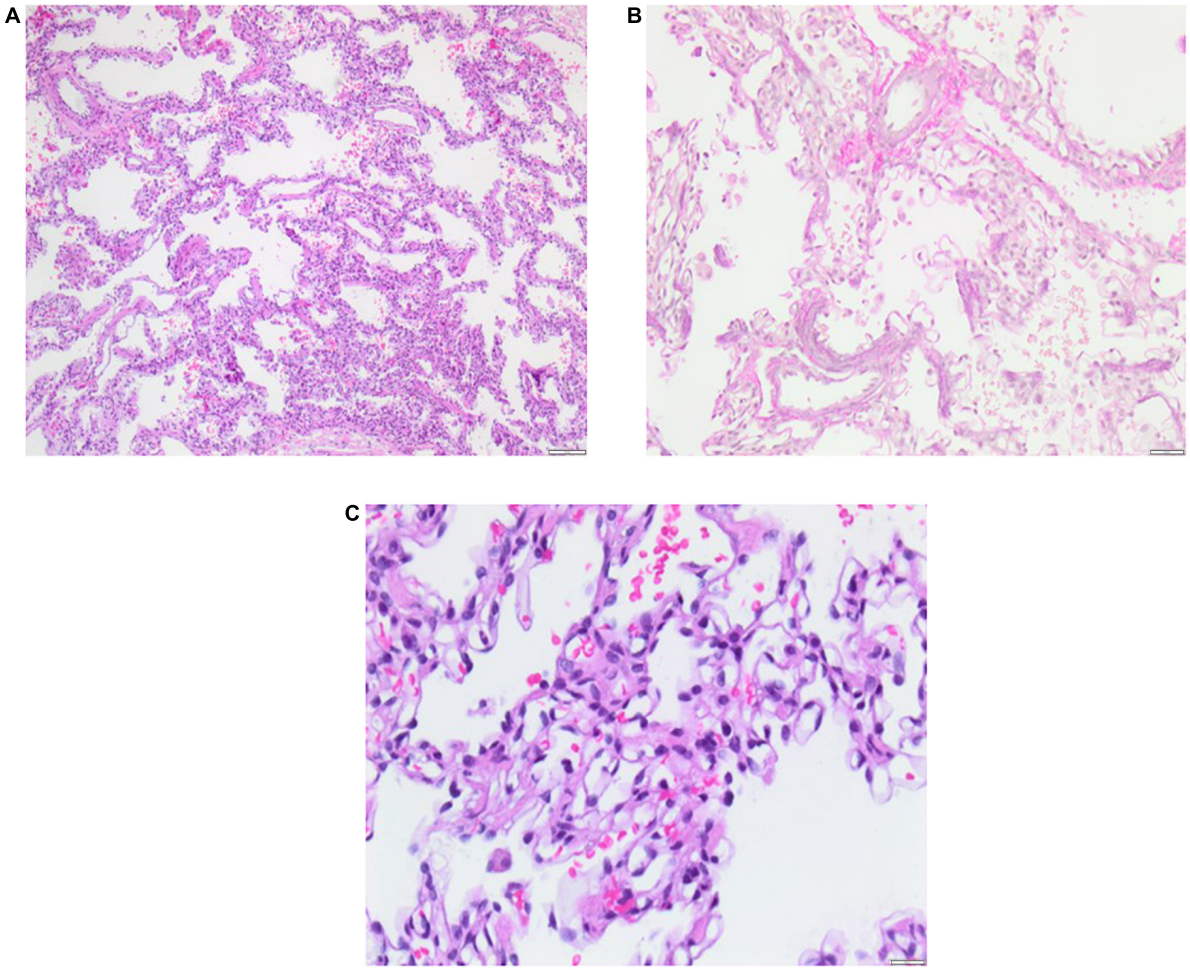

FIGURE 3
Lung biopsy 5 months after PICU discharge at the age of 11 months. Histology shows pulmonary capillary hemangiomatosis (PCH) without pulmonary venous involvement and mild pulmonary interstitial glycogenosis (PIG) with small foci. Severe bronchopulmonary dysplasia (BPD) is evident as alveolar simplification/hypoalveolarisation. Scale bar = 100 μm.

pulmonary hyperperfusion, patients are at risk of developing pulmonary edema, respiratory failure; they may also show abnormal remodeling of the pulmonary vascular bed with consecutive elevated PVR and chronic PH. Thus, we initiated pharmacotherapy with indometacin/ibuprofen for an early PDA closure without any success, so that the PDA ultimately had to be ligated surgically.

It is necessary to classify and unbundle BPD-PH and its sub-componentes through a diagnostic workup, whenever the patient is in stable cardiorespiratory condition. An accurate diagnostic workup, that may or may not include invasive lung biopsy, is essential for diagnosis. The histological findings are very relevant to understand primary or secondary pathologies in order to develop a sufficient treatment strategy. Lung biopsy represents the state of the art for diagnosis and classification of diffuse parenchymal lung disease (DPLD) or so called children's interstitial lung disease (chILD) in pediatric pulmonology (26). In our case, invasive examinations such as lung biopsy and RLHC were performed under general anesthesia once the patient was in stable cardiorespiratory condition. Histology (**Figure 3**) revealed crucial findings for accurate classification of DPLD, so DPLD/chILD was classified as (1) PCH with variable expression (group B4: DLPD-related to lung vessel structural processes), (2) mild small-hearted PIG (group A3: DPLD-Infant conditions of undefined etiology), and (3) severe BPD with hypoalveolarization (group A2: DPLD-Grwoth abnormalitites/alveolarization abnormalities). The main histological finding was PCH with proliferating capillaries, that partly infiltrated alveolar septal tissue.

Pulmonary capillary hemangiomatosis with or without obstruction of pulmonary venules was first described in 1978 as a pulmonary vascular pathology (27). The infiltration of

the excessively proliferating alveolar capillaries in alveolar septal tissue, bronchioles, and interstitial lung parenchyma plays an important role in the pathophysiology of PCH (28). The exact etiology of PCH is still not completely understood. Neoplastic processes and/or proliferation as a response to hypoxia are part of the assumed pathologic mechanisms (29). Currently, there is no curative therapeutic approach to PCH, rather, the disease has so far been treated with systemic steroids and vasodilative PH-targeted medication in case of PH. However, there is no standardized treatment strategy in children and infants with PCH, particularly due to the lack of published data on that topic. Fortunately, there was no pulmonary venous involvement in our patient in terms of a pulmonary veno-occlusive disease (PVOD). PVOD is characterized by obliteration of the small pulmonary venules through fibrotic thickening of the venous intima and irregular capillary proliferation (30), that lead to a progressive increase of PVR, PH and consecutive RV failure with high a mortality in patients with PVOD (31).

The patient of this report is currently treated with triple vasodilative and antiproliferative PH-targeted drugs. She also had intermittent systemic steroid pulses during exacerbations, which regularly and successfully led to a good cardiorespiratory condition. As of october 2022, no steroid pulses have been necessary for > 12 months, so that we can conclude that the underlying ChILD has substantially improved.

Generally, most antihypertensive PH-targeted drugs (except sildenafil and bosentan) are applied off-label in children with PH (14). Approval of PH-targeted drugs is limited mainly due to a lack of studies on the use of these drugs, especially in younger children and infants. Besides Sildenafil as a PDE5 inhibitor and Bosentan as an ERA, there is no data for the use of the other PH-targeted drug classes and their representatives for their application in BPD-PH (7). As in our case, macitentan is the primary ERA at our center and is preferred over bosentan mainly due to its less liver toxicity than bosentan, and therefore does not require regular liver function testing (blood draws) every 4 weeks. Furthermore, macitentan does not lower plasma sildenafil levels, as had been shown for bosentan. A prospective clinical phase 2 study on the safety, tolerability, and pharmacokinetics of selexipag in children is currently underway (estimated completion date: December 2026, trial ID: NCT03492177). Our prospective multicenter study on selexipag therapy in pediatric PH from 2020 (15) (n = 15, age range: 0.6–16.8 years) covered the safety and efficacy of selexipag in pediatric PH. Over 50% of the patient cohort showed a significant improvement in risk stratification, hemodynamic variables and physical activity after a median of 8 months add-on selexipag therapy. However, there is still no published data on selexipag treatment in preterm infants with BPD-PH. We started selexipag to support weaning off muscle relaxation, iNO and mechanical ventilation on pre-existing multiple antihypertensive PH-targeted drugs and circulatory support regimens. A decision was made to try oral selexipag based on our published multicenter study (15) first; as we expected it was much easier to discharge the patient as oral selexipag would allow for patient extubation, which was actually the case. IV epoprostenol or treprostinil would have been an option in severe PPHN or precapillary PH; but because we have seen patients with PVOD/PCH deteriorating quickly on IV treprostinil, we did not consider it suitable for the initial treatment. Although the diagnosis of PVOD/PCH was not confirmed at the start of selexipag initiation, another PH-targeted permanent drug with intravenous/subcutaneous administration (e.g., treprostinil) would have probably extended the stay in PICU, whereby the implantation of an intravenous/subcutaneous trepostinil-pump in an infant weighing < 5 kg would be hardly feasible. Regarding the clinical course, the transition from PICU to ICM is much easier with an oral prostacyclin agonist (selexipag) than with IV treprostinil. Furthermore, we already had positive experiences regarding oral selexipag therapy in pediatric patients with severe PAH (17). In case of further dependence on mechanical ventilation, the ultima ratio would have been the listing for bilateral lung transplantion with an uncertain outcome considering prematurity, young age, and poor general condition (dystrophy). Fortunately, we already had experience in our center with the use and side effects of selexipag in children with severe PH (15). In the current case, add-on Selexipag caused a rapid decrease in PVR with subsequent reduction in RV pressure loading and consecutive feasibility of extubation in stable cardiorespiratory conditions. Importantly, drug treatment with selexipag in small infants with severe PAH should be applied only in experienced centers and particularly in slow dose increases. Especially side effects such as peripheral vasodilation and decrease in systemic resistance and perfusion may result in multiple organ damage and limit therapy success. Another caveat is that an obstruction in the pulmonary capillary-pulmonary venous part of the circulation can not be excluded easily based on a chest CT or the clinical course, so that acute pulmonary edema can be a severe adverse event when using add-on Selexipag in this vulnerable patient population. Ultimately, the use and dose escalation of selexipag should be performed under regular blood pressure measurements and clinical monitoring, particularly regarding intestinal and renal function.

Conclusion

This first-in-infant report highlights the potential benefits of the orally available prostacyclin mimetic selexipag (IP receptor agonist) as an efficient add-on PH-targeted drug in infants with severe, chronic PH.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the patients' legal guardian.

Author contributions

HH collected data and wrote the first draft of the manuscript. GH initiated the report, collected data, and edited the manuscript. All authors read the manuscript, edited the manuscript for important intellectual content, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Christian Apitz,
Ulm University Medical Center, Germany

REVIEWED BY
Johannes Nordmeyer,
Klinik für kongenitale Herzkrankheiten Pädiatrische Kardiologie, Deutsches Herzzentrum Berlin, Germany
Omar R.J. Tamimi,
King Fahd Medical City, Saudi Arabia

*CORRESPONDENCE
Angela Bates
✉ abates@ualberta.ca

†These authors have contributed equally to this work

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A North American, single-center experience implanting fenestrated atrial devices and atrial flow regulators into a heterogeneous group of pediatric pulmonary hypertension patients

David Edward Youssef[1†], Konstantin Averin[2,3], Susan Richards[1], Catherine Sheppard[1], Cameron Seaman[2], Matthew Pietrosanu[4] and Angela Bates[1,5†*]

[1]Division of Pediatrics, Department of Pediatric Pulmonary Hypertension, Stollery Children's Hospital, Edmonton, AB, Canada, [2]Division of Pediatric Cardiology, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada, [3]Cohen Children's Heart Center, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, NY, United States, [4]Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB, Canada, [5]Division of Pediatric Critical Care, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

Introduction: The clinical deterioration commonly experienced by pediatric patients with pulmonary arterial hypertension (PAH) has motivated a shift in the treatment of pulmonary hypertension (PH) through innovations in surgical salvage interventions. The Occlutech fenestrated atrial septal defect (FASD) Occluder and the atrial flow regulator (AFR), which provides a protective, atrial-level shunt during hypertensive crises, have found an important role in treating pediatric patients with PAH. Other groups of pediatric patients with PH may also benefit from a similar protective physiology. The primary aim of this work is to present a single center's experience with AFR and FASD devices for managing a heterogeneous group of pediatric PH patients. A secondary goal is to identify hemodynamic changes and complications following device implantation.

Materials and Methods: We performed a retrospective review of all pediatric PH patients who, after being found suitable, either successfully or unsuccessfully received an FASD or AFR device between January 2015 and December 2021 at the Stollery Children's Hospital in Edmonton, Canada.

Results: Fourteen patients (eight female) with a median age of 4.6 (range 0.3–17.9) years and a median body mass index of 15.1 ($Q_1 = 13.8$, $Q_3 = 16.8$) kg/m^2 underwent device implantation: five received FASDs, eight received AFRs, and one was ultimately unable to receive an implant due to thrombosed iliac vessels and required surgical intervention. Of the fourteen patients, seven were in group 1 (PAH), one was in group 3 (lung disease), and six were in group 5 (primarily pulmonary hypertension vascular disease) under the World Symposium PH classification. All patients were on mono-, dual-, or triple-drug PH therapy. Device stabilization was not possible for two patients, who then required a repeat catheterization. Of the group 1 patients, three AFR and three FASD implants were successful, while one FASD implant was unsuccessful due to thrombosed vessels. At a six-month clinical assessment, all group 1 patients had patent devices and improved WHO FCs.

Conclusion: This work presents a single center's experience with AFR and FASD implants in a heterogeneous group of fourteen pediatric patients with severe PH. This treatment strategy is novel in the pediatric population and so this work provides momentum for future studies of interventional cardiac catheterization procedures for pediatric patients with PH. Further collaborations are required to develop criteria to identify ideal pediatric candidates and optimally time interventions in order to maximize the benefits of this treatment.

KEYWORDS

atrial flow device, atrial septal defect, interventional procedures, hypertensive crisis, vasodilator therapy

Introduction

Pulmonary arterial hypertension (PAH) is a severe, irreversible, and progressive disease that involves destruction to the pulmonary vascular bed, increases in right-ventricular pressure, and eventual failure of the right ventricle. All these factors contribute to the disease's high long-term morbidity and mortality (1). Pivotal to the management of pulmonary hypertension (PH) are early and aggressive treatments that aim to improve patient quality of life and reduce mortality. Over the past few decades, the epidemiology of pediatric PH has been changing: while the rates of idiopathic and heritable PAH have remained stable, those for PAH associated with congenital heart disease, PAH secondary to developmental lung disease, and pulmonary hypertensive vascular disease (PHVD) have increased (2).

Despite advances in treatment options that target multiple pathways, many patients deteriorate even when on combination therapy. This leads to frequent and prolonged hospitalizations, a progressive decline in quality of life, and increased morbidity and mortality. Previous work in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) study estimated the five-year survival time from diagnosis for children under 18 years of age to be 74%; patients diagnosed at an older age had a worse prognosis (3). There has consequently been a shift toward aggressive medical management strategies (including the early use of dual and triple therapy) and greater need for treatment-resistant options for patients with PAH.

The advantages and disadvantages of an atrial septal defect (ASD) are often difficult to determine for pediatric PH patients. This determination can be even more challenging among group 3 patients with developmental lung disease, where even a small shunt might not be well tolerated by the vulnerable developing pulmonary vascular bed. For some patients, the benefit of closing an ASD to minimize excess left-to-right shunting is balanced by the protective effect of right-to-left shunting during pulmonary hypertensive crisis or syncope (4–6). Failure of the right ventricle is associated with acute elevation of pulmonary arterial pressure (PAP) from baseline. Increased PAP, especially if sudden and significant, further leads to an increase in right-ventricular end diastolic pressure (RVEDP) and a subsequent elevation of right-atrial pressure (RAP), dilation of the right ventricle, bowing of the interventricular septum into the left ventricle, and an increase in left-ventricular end diastolic pressure. Associated sequelae are signs and symptoms of acute right ventricle failure, decreased cardiac output, coronary artery perfusion, and cerebral perfusion leading to cardiac arrest (**Supplementary Figure S1**). The creation of a controlled atrial fenestration with an atrial flow regulator (AFR) can decrease RAP and offer a right-to-left shunt, increase cardiac output to the left side, and decrease RVEDP and right ventricle dilation. This strategy both offloads the right ventricle and improves systemic cardiac output with the consequence of mild desaturation (6).

Until recently, the only options available to children were surgical ASD closure with a residual fenestration; percutaneous closure with a modification of an existing device; or, for patients with an intact atrial septum, a balloon atrial septostomy. All of these approaches are suboptimal (3). The Occlutech atrial flow regulator (AFR) and the fenestrated ASD (FASD) Occluder allow for the creation or maintenance of stable interatrial communication in patients with PAH. These purpose-made devices allow for atrial communication or reduce the size of an ASD without the need for cardiopulmonary bypass or the downsides of modified percutaneous devices.

Reports on the implantation of these devices in the pediatric population are limited to the works noted in **Supplementary Table S1**. Even more scarce are reports on experiences with these devices among group 1 and group 5 patients, especially with regard to patient selection and timing. Growing experience suggests two types of vulnerable group 1 patients: those who benefit from an AFR, which creates an ASD and protects the right ventricle, and those who benefit from an FASD, which minimizes ASD size and allows pulmonary vasodilator therapy to be optimized. Nonetheless, the literature is still limited regarding patient selection and outcomes (7–12).

This work presents a single-center experience of a heterogeneous group of pediatric patients who underwent a catheter-based procedure with AFRs and FASDs. Herein we present patient demographics, PH diagnoses and etiologies, and acute- and mid-term outcomes following intervention. The primary aim of our work is to examine a single center's experience with AFR and FASD devices for managing pediatric PH. A secondary goal is to identify changes in hemodynamics and functional classification as well as complications following device implantation.

Materials and methods

We present a retrospective, single-center experience of all PH patients who underwent ASD closure with an FASD or atrial shunt creation with an AFR between January 2015 and December 2021 at the Stollery Children's Hospital in Edmonton, Canada.

Demographic and clinical details including sex, age at device implantation, device type and size, clinical indications, PH

classification, and genetic conditions were collected at baseline. Information on pulmonary vasodilator therapy regimens and additional medications at the time of intervention (including anticoagulants/antiplatelets), hemodynamic data prior to and immediately following device implantation, clinical characteristics, vital signs, results from the six-minute walk test, and echocardiographic parameters prior to implantation and at six months post-intervention were also collected.

Decision pathway and patient eligibility

The decision pathway for the patients in this study made use of imaging data (e.g., echocardiography, computed tomography, cardiac magnetic resonance imaging), 12-lead electrocardiogram data, six-minute walk test results where appropriate, laboratory data (including that on NT-proBNP and liver function), and a medication review. All patients were discussed at a joint cardiac surgical conference with representation from cardiology, pediatric cardiothoracic surgery, and interventional cardiology. A patient was deemed to be suitable if the following criteria were met.

- A group 1 patient must have worsening PH symptoms including PH crises, syncope, an inability to augment pulmonary vasodilator therapy, or reduced exercise tolerance despite optimal PH vasodilator therapy. All patients were on optimal or maximal PH therapy.
- A group 5 patient (with single-ventricle physiology following cavopulmonary anastomosis or Fontan completion) must have remained desaturated and have evidence of elevated pulmonary vascular resistance or hypoxemia.

Patients were excluded if the joint decision was that the patient was unsuitable for implantation under the following criteria.

- Atrial communication was unfavorable based on multimodal imaging.
- The procedure was likely to be unsuccessful secondary to the probable etiology of PH.
- The risk of the procedure outweighed the benefit as determined by the multidisciplinary team.
- A patient was unsuitable based on atrial septal morphology or if a preoperative assessment medication review took place in association with a pediatric pharmacist and medication was optimized or modified.

Technical details and follow-up

No patients received a cardiac catheterization prior to the joint cardiac surgical decision as multimodal imaging was employed for a cardiac assessment. Following a decision to proceed with implantation, a cardiac catheterization was performed under general anesthesia by a cardiac anesthetist familiar with managing pediatric PH patients. All patients received a preprocedure PH assessment by our PH team, cardiac anesthetists, and the pediatric cardiac intensive care unit. All patients, caregivers and parents were counseled by the members of the multidisciplinary team. Ample opportunity was allowed to assess, seek, and review any concerns related to the procedure.

A standard technique with a Brockenbrough trans-septal needle was utilized to perform a trans-septal puncture (typically a 7F Mullins trans-septal sheath) with subsequent static and cutting balloon angioplasty of the atrial septum to 150%–200% of the intended AFR size (e.g., pre-dilation to 8 mm for a 4 mm AFR implant). Final sheath size was determined by that required for the AFR device. Therapeutic heparin was used as a bridge to dual antiplatelet therapy for all devices.

Following device implantation, all patients received regular structured follow-ups that included clinical, imaging (echocardiographic), and laboratory assessments. Cardiac catheterization and hemodynamics were obtained under resting conditions with normal gas exchange (pH 7.35–7.45 and $paCO_2$ 35–45 mmHg). Where possible, the following measurements were obtained:

- systolic, mean, and diastolic systemic arterial pressures;
- right-arterial pressure;
- right-ventricular systolic end-diastolic pressure;
- systolic, mean, and diastolic mean pulmonary arterial pressure (mPAP);
- pulmonary arterial wedge pressure (PAWP);
- left-atrial and left-ventricular end-diastolic pressure;
- transpulmonary gradients, simultaneous PAWP, and end-diastolic pressure; and
- cardiac index and pulmonary vascular resistance index *via* standardized formulas based on hemodynamic measurements (2, 13).

All patients, even those for whom devices were not successfully deployed, were included. As the devices used are not approved for commercial use by Health Canada, approval was granted through the Health Canada Special Access Program *via* an application for each patient. Ethics approval was obtained from the Health Research Ethics Board at the University of Alberta (Pro00116783).

Statistical analysis

Statistical analyses were performed using R version 3.6.3 (14). Categorical data are summarized with counts and relative percentages, and numerical data with the first through third quartiles. Paired Wilcoxon signed-rank tests are used to compare pre- and post-implantation measures. Raw *p*-values are presented throughout. A significance level of 0.05 is used in all subsequent interpretations.

Results

Cohort characteristics

In total, fourteen patients (eight females and six males) received either an FASD or ASD between January 2015 and December 2021. Two patients underwent repeat catheterizations at different dates; these patients are each represented as a single record. See **Supplementary Table S2** for more detail. Patients' clinical characteristics and hemodynamics at baseline are summarized in **Table 1**: median age at implantation was 4.6 (range 0.3–17.9)

TABLE 1 Baseline demographics and clinical measures for All fourteen patients, presented as median (Q_1, Q_3) or count (%).

Variable/level	Summary
Sex	
Male	6 (42.9%)
Female	8 (57.1%)
Age and anthropometrics	
Age (years)	4.6 (1.9, 8.6)
Weight (kg)	16.4 (8.3, 22.2)
Height (cm)	107.8 (82.5, 124.3)
Body mass index (kg/m^2)	15.1 (13.8, 16.8)
WSPH classification	
Group 1 (PAH)	7 (50.0%)
Idiopathic PAH	4 (57.1% of group 1)
PAH-CHD	3 (42.9% of group 1)
Group 3 (lung disease)	1 (7.1%)
Group 5 (PHVD)	6 (42.9%)
Clinical/biomedical profile	
O_2 saturation (at rest) (%)	92.0 (85.5, 96.5)
NT-proBNP (ng/l)	2884.0 (1217.0, 11,256.0)

NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PAH-CHD, pediatric arterial hypertension associated with congenital heart disease.

years, median body mass index was 15.1 ($Q_1 = 13.8$, $Q_3 = 16.8$) kg/m^2, median oxygen saturation at rest was 92.0% ($Q_1 = 85.5\%$, $Q_3 = 96.5\%$), and median baseline NT-proBNP was 2884.0 ($Q_1 = 1217.0$, $Q_3 = 11{,}256.0$) ng/l. For morphometric measures, diagnoses, clinical indications, therapies, and medications at the individual level, see **Supplementary Table S2**.

The cohort contained seven patients in group 1 (PAH) (four with idiopathic PAH and three with PAH associated with congenital heart disease), one in group 3 (lung disease), and six in group 5. The patients in group 5 predominantly had single-ventricle physiology with Fontan circulation and PHVD (transpulmonary gradient greater than 7 mmHg and/or pulmonary vascular resistance index above 3 iWU). The majority of these patients had hypoplastic left heart syndrome. One of the group 5 patients had pulmonary atresia with an intact ventricular septum and major aortopulmonary collateral arteries; an FASD device was inserted in a hypoxemic setting to minimize flow across the atrial septum. This patient was unique among the patients with single-ventricle indications. While this patient had PHVD by definition, the FASD was placed due to hypoxemia in the atrial septum position. One patient had trisomy 21 and one had DiGeorge syndrome (*22q11.21–q11.23*). There was one variant of unknown significance and one copy number variation (*12 p11.21*). All patients, except one who underwent successful device implantation, received anticoagulant therapy immediately after device deployment for shunt preservation. Five of the patients were on diuretic therapy both before and after device implantation.

Difficult device implantations

Two patients each required two separate cardiac catheterizations. The device originally received by Patient 2 embolized shortly after deployment but was successfully retrieved and removed with no ill effects. Six months later, the patient returned and received a larger FASD implant. Patient 4's fenestration spontaneously closed shortly after the intervention and a larger device was implanted successfully at a later date.

Device deployment was unsuccessful for patients 13 and 14. Patient 13's device could not be implanted due to bilateral femoral venous occlusion. Device deployment for Patient 14 (five months old at the time of intervention) was not successful due to a moderate ASD: the device embolized to the left atrium and left ventricle on the first and second attempts, respectively. The device was successfully retrieved after each attempt and, ultimately, the infant received a surgical ASD closure.

Clinical, hemodynamic, and echocardiographic impact

We observed a statistically significant improvement in WHO functional classification (WHO FC) among all patients ($p = 0.018$): in our cohort, five patients (all class III pre-implantation) were reclassified into class II and two patients (one in each of classes III and IV pre-implantation) were reclassified into class I. The other patients remained in one of class II or III over the study period. No patients worsened with respect to WHO FC. The distributions of pre- and post-implantation WHO FC are shown in **Figure 1** for all patients and in **Table 2** for group 1 patients.

Significant pre–post differences in hemodynamic measures were not detected among group 1 PAH patients: these results are summarized in **Table 2**. A decrease in median right-ventricular systolic pressure (RVSP) from 40.0 mmHg to 26.5 mmHg was

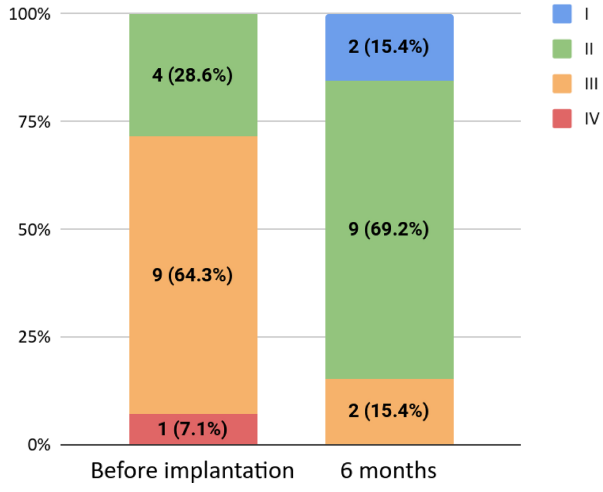

FIGURE 1
WHO functional classifications before and six months after implantation. The latter was not available for one patient.

TABLE 2 Pre and post measures for the seven group 1 patients, presented as median (Q_1, Q_3) or count (%).

Variable	Pre measure[1]	Post measure[1]	*P*-value[2]
Clinical/biochemical profile[3]			
NT-proBNP (ng/l)	2284.0 (2023.0, 5656.0)	-	-
SpO_2 (at rest) (%)	97.0 (94.0, 99.5)	-	-
SpO_2 (during exercise) (%)	93.0 (92.5, 93.5)	-	-
Hemodynamics[4]			
CI (mL/min/m^2)	3.8 (3.2, 4.2)	3.7 (3.0, 3.9)	0.25
mPAP (mmHg)	24.0 (24.0, 39.0)	30.5 (22.8, 37.3)	0.18
PCWP (mmHg)	7.0 (6.0, 8.0)	7.0 (5.8, 8.3)	1.00
PVRI (WU m^2)	4.7 (4.6, 7.0)	5.1 (3.5, 7.4)	0.13
RAP (mmHg)	5.0 (4.0, 5.0)	3.0 (2.5, 3.5)	-
RVSp (mmHg)	40.0 (35.0, 54.0)	26.5 (25.3, 27.8)	-
Echocardiography[5]			
PAAT (ms)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	-
RVFAC (%)	38.3 (37.4, 39.8)	43.5 (40.4, 46.2)	0.59
RVSP (mmHg)	45.0 (39.0, 63.0)	54.0 (45.5, 54.5)	-
TAPSE (cm)	2.0 (1.8, 2.7)	1.9 (1.7, 2.2)	0.85
TV e′ (cm/s)	11.2 (9.1, 15.3)	13.0 (12.4, 15.2)	-
TV s' (cm/s)	12.8 (11.4, 14.5)	11.1 (10.5, 11.1)	-
WHO FC			
Class I	0 (0.0%)	2 (33.3%)	0.18
Class II	2 (28.6%)	3 (50.0%)	
Class III	4 (57.1%)	1 (16.7%)	
Class IV	1 (14.3%)	0 (0.0%)	

CI, Cardiac index; NT-proBNP, N-terminal pro B-natriuretic peptide; PAAT, pulmonary arterial acceleration time; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; RAP, right-atrial pressure; RVFAC, right-ventricular fractional area change; RVSP, right-ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TV e' and TV s' are indices of tissue doppler velocities of the tricuspid valve.

[1]Clinical/biomedical measurements, echocardiographic measurements, and WHO FC were obtained at baseline and six months after implantation. Hemodynamic measurements were made before and immediately after implantation.

[2]Comparisons are not conducted with two or fewer pre–post measurement pairs. For the available comparisons, $n = 4$ except for CI ($n = 3$) and WHO FC ($n = 6$).

[3]For SpO_2 (during exercise), $n = 2$. For SpO2 (at rest) and NT-proBNP, $n = 7$. No corresponding post data was available.

[4]For pre hemodynamic measurements, $n = 5$ except for CI ($n = 3$). For post hemodynamic measurements, $n = 2$ for CI and RAP; $n = 3$ for CI; and $n = 4$ for mPAP, PCWP, and PVRI.

[5]For pre echocardiogram measurements, $n = 1$ for PAAT, $n = 6$ for RVFAC, $n = 5$ for RVSP, $n = 7$ for TAPSE, and $n = 4$ for TV e' and TV s'. For post echocardiogram measurements, $n = 2$ for PAAT, $n = 4$ for RVFAC, $n = 3$ for RVSP, $n = 4$ for TAPSE, and $n = 3$ for TV e' and TV s'.

observed. Median cardiac index was comparable pre- and post-implantation at 3.8 L/m^2 and 3.7 L/m^2, respectively.

No statistically significant changes were detected in echocardiographic or tissue doppler imaging parameters between pre- and post-implantation for patients in group 1. We observed an increase in median RVSP from 45.0 mmHg to 54.0 mmHg and a decrease in median tricuspid annular plane systolic excursion (TAPSE) from 2.0 cm to 1.9 cm. We observed an improvement in median right-ventricular fractional area change (RVFAC) from 38.3% to 43.5%. These results are summarized in Table 2.

Discussion

This work represents a single center's experience with AFRs and FASDs in a heterogeneous group of fourteen pediatric patients with severe PH, among which twelve had successful implantations. The two unsuccessful implantations were due to device embolization and thrombosed iliac vessels that prohibited femoral vascular access. The majority of the cohort had devices that were patent at six months post-implantation. We observed improvements in various echocardiographic measures, but none of these pre–post comparisons were statistically significant: we attribute this in part to the small size of the cohort and the lack of consistently available data. On the other hand, we observed a statistically significant improvement in WHO FC across the entire cohort: seven patients saw an improvement in their classification post-implantation. Thirteen of the patients were alive after a mean follow-up time of 17.4 months. This work is the largest single-center experience in children of AFRs and FASDs in the pediatric population: see Supplementary Table S1 for a summary of related literature.

Three factors are recognized as contributing to PH associated with ASDs: the size of the ASD, the location of the ASD, and associated syndromes and lesions. Interplay between the size of the defect and the compliance of the right ventricle predicts the potential for right-ventricular volume overload stemming from a left-to-right shunt (2). By Poiseuille's law, pulmonary pressure is the product of pulmonary blood flow and pulmonary vascular resistance (15). Therefore, in children with systemic-to-pulmonary shunts (i.e., ASDs), increased left-to-right shunting at the atrial level causes an increase in pulmonary blood flow, which subsequently leads to progressive vascular changes, increased shear stress, smooth muscular hypertrophy, and endothelial dysfunction (16). Although this is not the only contributing factor in the development of PAH, interventions such as AFRs and FASDs modify the elevation of PAP stemming from flow and shear stress and reduce the potential for further vascular remodeling. FASDs allow vasodilator therapy to modify disease progression and improve patient quality of life. In our cohort, the clinical benefits of AFR and FASD implantation were clinically (but not statistically) significant among patients in group 1. At follow-up, three of these patients were reported to be effectively utilizing their atrial shunts and reported fewer syncopal events relative to before implantation.

Group 5 (PHVD) patients require separate mention although they are not the primary focus of the current work. It is recognized that patients with Fontan physiology who have elevated cavopulmonary pressures have poorer survival outcomes and that the creation of a fenestration to augment elevated right ventricle or cavopulmonary pressures improves survival. However, this comes at the expense of lower systemic oxygen saturations. In addition, patients who have too large a fenestration and require a reduction

in fenestration size to improve systemic oxygen saturations without a complete obliteration of the fenestration would also benefit from such a device. In our cohort, six patients had Fontan circulation. The role of the devices among the patients in group 5 included fenestration reduction in two cases, fenestration occlusion in two cases, and fenestration creation in two cases. While the focus of our work is not on this subgroup in particular [e.g., similar to the work by O'Callaghan et al. (17)], we noted improvements in oxygen saturation and WHO FC at follow-up. While in the work by O'Callaghan, five of the six pediatric patients had failing Fontans, our cohort only included one patient with a failing Fontan. Three of the six group 5 patients required closure or fenestration size reduction for systemic desaturation. Our work adds to the current literature regarding the unique and complex subset of group 5 patients with single-ventricle physiology. For these patients, the combination of pulmonary vasodilator therapy and interventional procedures as described above should in theory improve survival.

In adherence to current guidelines from the American Heart Association and American Thoracic Society, the patients in our cohort were provided with individualized treatments. Each patient was considered from a multidisciplinary perspective and received recommendations from a cardiologist, a team of PH specialists, and an interventional cardiologist. An individualized approach was required for each patient prior to choosing the device to implant.

Current literature on the use of AFRs and FASDs is limited to small case series and case reports, as shown in **Supplementary Table S1**. Kaley et al. (18) considers thirty-five device implantations, including six for pediatric patients with severe PAH. Of those patients, four were on dual therapy and two were on triple therapy. There was a 93% deployment success rate in their cohort. One pediatric mortality was reported secondary to progressive PAH one month after successful device implantation. At immediate and long-term follow-up, the other five children were observed to have symptoms consistent with the New York Heart Association's (NYHA's) class II categorization without the recurrence of syncopal episodes as well as an improvement in six-minute walk test results. Rajeshkumar et al. (19) considers twelve patients (aged 15–39 years) and demonstrates the benefits of atrial septostomy using AFR devices for patients on dual therapy (phosphodiesterase type-5 inhibitors and endothelin antagonists). The authors noted significant improvements in symptoms, six-minute walk test distance, cardiac index, and systemic oxygen transport. This is consistent with our study, which found patent atrial shunts and improvements in WHO FC. While we observed improvements in echocardiographic measurements post-implantation, we could not establish the statistical significance of these differences: we attribute this to the size of and availability of data within our cohort.

This is one of the first studies to describe an experience with AFRs and FASDs in a group of pediatric patients with severe PH. Although we observed improvements in objective and subjective parameters, the long-term benefits of this therapy are yet to be conclusively established. We recognize the limitations of this retrospective study, which include the small sample size, the lack of a comparator arm, and the heterogeneous patient group. As such, further work and collaboration (e.g., among international registries) is needed to increase knowledge and understanding of the role of atrial devices in managing pediatric PAH. Future work such as prospective, multicenter collaborations should consider the problem of identifying pediatric patients who should undergo device implantation and the optimal timing of these interventions. While the current work is retrospective, the decisions regarding individual patients are not known to the authors of the present work. While it would be insightful to know the decision algorithm for each individual patient, this information was not available for this retrospective review. Further prospective work is needed to guide future work.

Due to the technical details and the high level of expertise needed, the interventions described in this work should ideally be performed in pediatric PH centers given the high risk and potential for PH patients to decompensate with minimal provoking stimulus. Further details regarding technical parameters, including access sites, the complexities of implantation during deployment, and procedures to cross the atrial septum, go beyond the scope of the current work. Further multicenter and collaborative work is planned to explore the utility and potential of this procedure in the pediatric population.

Conclusion

This work presents a single center's experience with AFRs and FASDs in a heterogeneous group of fourteen pediatric patients with severe PAH and demonstrates the range of PAH patients that can benefit from these devices. Among group 1 patients, clinical improvements in objective and subjective parameters were evident at six months following the intervention. Further multicenter work is required to develop criteria for identifying ideal pediatric candidates and set optimal intervention timing in order to maximize the clinical and symptomatic benefits of this treatment.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics approval was obtained from the Health Research Ethics Board at the University of Alberta (approval number Pro00116783). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors have read and approved the final manuscript. DY, SR, CS, and WH were responsible for study screening and data extraction. MP was responsible for data analysis and copy editing. DY and AB

were responsible for writing the manuscript. KA and CS were responsible for checking and reviewing the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1073336/full#supplementary-material.

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EDITED BY
Christian Apitz,
Ulm University Medical Center, Germany

REVIEWED BY
Usha Krishnan,
Columbia University Irving Medical Center, United States
Michal Odermarsky,
Skåne University Hospital, Sweden

*CORRESPONDENCE
Angela Bates
✉ abates@ualberta.ca

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Multicenter review of a tadalafil suspension formulation for infants and children with pulmonary hypertension: A North American experience

David Edward Youssef[1], Stephanie S. Handler[2], Susan Marjorie Richards[1], Catherine Anne Sheppard[1], Jenna Smith[3], Kathryn Tillman[2], Matthew Pietrosanu[4], Edward Kirkpatrick[2] and Angela Bates[1,5]*

[1]Division of Pediatrics, Department of Pediatric Pulmonary Hypertension, Stollery Children's Hospital, Edmonton, AB, Canada, [2]Division of Pediatric Cardiology, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI, United States, [3]Department of Pharmacy, Stollery Children's Hospital, Edmonton, AB, Canada, [4]Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB, Canada, [5]Division of Pediatric Critical Care, Division of Pediatrics, University of Alberta, Edmonton, AB, Canada

Introduction: Phosphodiesterase type 5 (PDE5) inhibitors, with sildenafil the earliest among them, are widely used in the management of pediatric pulmonary arterial hypertension (PAH). Tadalafil is a PDE5 inhibitor with a long half life (16 h), stable pharmacokinetics and pharmacodynamics, and minimal adverse effects. However, the utility of tadalafil suspensions in this setting has not been widely explored due to a lack of clinical experience. We present a multicenter experience that details the safety and tolerability of a tadalafil suspension, either alone or in combination with another vasodilator, for the management of pediatric pulmonary hypertension (PH).

Methods and materials: This is a retrospective chart review of infants and children at Children's Wisconsin and the Stollery Children's Hospital enrolled in pediatric PH programs between December 2013 and April 2022 managed with a tadalafil suspension. Patients aged six years of age and under who were treated with a tadalafil suspension were included. Demographics, clinical information, echocardiographic and hemodynamic measurements, and laboratory data were collected before and six months after tadalafil initiation.

Results: Over the study period, 154 children with a median age of 1.0 (range 0.0–6.9) years were treated with tadalafil therapy. Of these, 39 (25.3%) were in group 1 (PAH), 79 (51.3%) were in group 3 (lung disease), and 33 (21.4%) were in group 5 (pulmonary hypertensive vascular disease). The median initial dose of tadalafil was 1.0 mg/kg once daily. Eleven (7.1%) patients in the cohort were established on tadalafil therapy *de novo*. The suspension formulation was necessary for 103 (66.9%) patients due to an inability to take enteral tablets and for 49 (31.8%) due to a need for feeding *via* gastric or jejunal tubes. We observed a statistically significant increase in tricuspid annular plane systolic excursion as well as significant decreases in right-ventricular systolic pressure and NT-proBNP. Tadalafil therapy was well tolerated over the six-month period: at six months, no adverse effects were reported aside from gastrointestinal disturbances by 2 (1.3%) patients.

Conclusion: Tadalafil, a long-acting PDE5 inhibitor, when administered in a suspension formulation, has a safe and tolerable adverse effect profile. Following six months of therapy, our cohort showed improvements in clinical parameters, echocardiographic measurements, and laboratory results. Patient compliance was good and adverse effects were rare, minor, and manageable with nonpharmacological means.

KEYWORDS

adverse effect, echocardiography, hemodynamic, pulmonary vasodilator, safety, tolerability

Introduction

Pulmonary hypertension (PH) is a progressive disease that results in right heart failure and has a high mortality among severe cases. Advancements in the treatment of pediatric PH, which have followed drug approvals for adults with pulmonary arterial hypertension (PAH), have improved quality of life and survival for pediatric patients. Therapy targeting multiple pharmacological pathways such as the nitric oxide, endothelin, and prostacyclin pathways are now available in at least four formulations (i.e., oral, inhaled, subcutaneous, and intravenous) (1–3).

All available oral therapies originated in pill form; several of these have been adapted for young pediatric patients who cannot take pills due to age or the need for administration through an enteral feeding tube. One such oral agent, the selective phosphodiesterase type 5 (PDE5) inhibitor tadalafil, was approved by the FDA for use in adults with PAH in 2009.

Tadalafil's application to adult PAH has led to significant improvements in patient exercise capacity and quality of life. Accordingly, tadalafil has since been more widely used in the pediatric population (2, 3). Tadalafil's relatively long half life and once-daily dosing facilitates improved compliance and reduced serum drug concentrations relative to sildenafil (4, 5). Compound tadalafil suspensions have permitted further flexibility with regard to dosing and administration in infants and children.

However, experiences with tadalafil suspensions in monotherapy or combination therapy for pediatric PH are not widely available in the literature. The purpose of this study is to describe the use of an enteral tadalafil suspension in two large North American pediatric PH centers. Specifically, our primary goal is to describe the safety and tolerability of tadalafil suspensions for infants and children six years of age and under with PH. Our secondary goal is to demonstrate the safety and clinical utility of transitioning from enteral sildenafil to an enteral tadalafil suspension that has previously been presented in the literature (6).

Materials and methods

This is a retrospective, descriptive, two-center study analyzing clinical and echocardiographic data collected from infants and children six years of age and under enrolled in the pediatric PH programs at the Stollery Children's Hospital from January 1, 2014 to April 30, 2022 and at Children's Wisconsin from December 11, 2013 to March 8, 2022 and managed with a tadalafil suspension. We collected data on patient demographics, clinical characteristics, PH diagnoses following the 6th World Symposium on Pulmonary Hypertension (WSPH6) (directly from clinical notes), tadalafil dosing, prior and concurrent treatments, adverse effects and treatment tolerability, and echocardiographic parameters based on center-specific protocols and biochemical measures before and six months following tadalafil initiation. Children's Wisconsin was not able to provide some echocardiographic parameters.

Echocardiographic parameters were obtained under the institutions' pediatric PH protocols. Imaging was obtained from subcostal, apical 4 chamber, parasternal long-axis, and parasternal short-axis views. Information on shunt size and direction was retrieved wherever possible. Right-ventricular systolic pressure was calculated as the sum of tricuspid regurgitation velocity and right-atrial pressure. Eccentricity index was calculated from the parasternal short-axis view as the ratio between the major and minor dimensions of the left ventricle at end systole and at the papillary muscle level. Right-ventricular fractional area change in systole and diastole at the basal, papillary, and apical levels were calculated from an optimized right ventricle view. Right–left ventricle diameter ratio was obtained at end systole. Mean pulmonary arterial pressure was estimated from end-diastolic pulmonary insufficiency. All patients were treated under the same standardized PH protocol at both institutions. Patients were not included if they were not treated with a tadalafil suspension as part of their treatment strategy.

Ethics approvals were obtained from the Health Research Ethics Board at the University of Alberta (Pro00120489) and the Institutional Review Board at Children's Wisconsin (1704191-3).

Statistical analyses were performed using R version 3.6.3 (7). Categorical data are summarized with counts and percentages, and numeric variables with the first through third quartiles. Paired pre–post comparisons were conducted using paired Wilcoxon signed rank tests; corresponding p-values are adjusted (across the main text) with a Benjamini–Hochberg correction for false discovery. We use a threshold significance of 0.05 throughout.

Results

Patient cohort

Over the study period, 154 patients were treated with tadalafil. Of these, 72 (46.8%) were female. The median age at the initiation of tadalafil therapy was 1.0 (range 0.0–6.9) years (**Figure 1**) with a median BMI of 15.3 ($Q_1 = 14.2$, $Q_3 = 16.8$) kg/m^2. Of the 154 patients, 4 (2.6%) went on to require transplantation and 146 (94.8%) were alive at a six-month evaluation. In terms of ethnicity, 99 (64.3%) patients were Caucasian, 23 (14.9%) were Black, 10 (6.5%) were Indigenous, and 10 (6.5%) were Asian. Trisomy 21 was documented in 21 (13.6%) patients, DiGeorge syndrome in 3 (1.9%), and trisomy 18 in 4 (2.6%). See **Table 1** for more detail regarding the demographics, anthropometrics, and genetic conditions of our cohort.

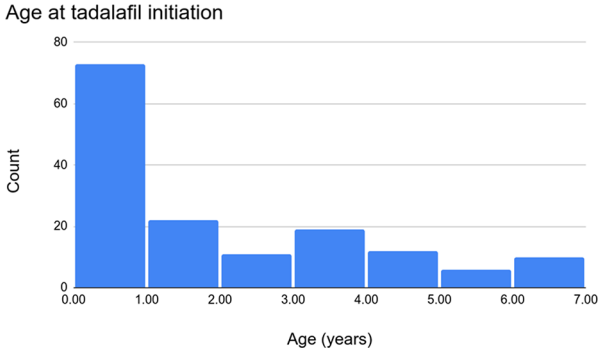

FIGURE 1
Histogram of age at tadalafil initiation.

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TABLE 1 Patient demographic and clinical characteristics at tadalafil initiation, summarized as median (Q_1, Q_3) or count (%).

Variable/level	Summary
Demographics/anthropometry	
Sex: female	72 (46.8%)
Age (years)	1.0 (0.5, 3.1)
Weight (kg)	7.9 (5.7, 13.0)
Height (cm)	71.8 (59.9, 94.2)
BMI (kg/m^2)	15.3 (14.2, 16.8)
Ethnicity	
Asian	10 (6.5%)
Black	23 (14.9%)
Caucasian	99 (64.3%)
Indigenous	10 (6.5%)
Other	12 (7.8%)
Genetic syndromes	
DiGeorge syndrome	3 (1.9%)
Noonan syndrome	3 (1.9%)
Trisomy 18	4 (2.6%)
Trisomy 21	21 (13.6%)
Other	9 (5.8%)
WSPH6 classification	
Group 1	39 (25.3%)
Group 2	1 (0.6%)
Group 3	79 (51.3%)
Group 4	1 (0.6%)
Group 5	33 (21.4%)

Under the WSPH6 diagnostic classification, 79 patients (51.3%) were in group 3, 39 (25.3%) were in group 1, 33 (21.4%) were in group 5, 1 (0.6%) was in group 2, and 1 (0.6%) was in group 4.

Effect of tadalafil on functional capacity

Among the 131 patients with a WHO functional class (WHO FC) available at baseline, 57 (43.5%) were in class IIIa, 39 (29.8%) were in class II, 24 (18.3%) were in class I, 8 (6.1%) were in class IIIb, and 3 (2.3%) were in class IV. Among these patients, 130 had a WHO FC available six months after tadalafil initiation: 70 (53.8%) were in class II, 44 (33.8%) were in class I, 13 (10.0%) were in class IIIa, 2 (1.5%) were in class IIIb, and 1 (0.8%) was in class IV (**Supplementary Table S1**). These distributions are shown in **Figure 2**.

Tadalafil dosing and adverse effects

The majority of patients were transitioned from sildenafil to tadalafil; only 11 (7.1%) patients started liquid tadalafil *de novo*.

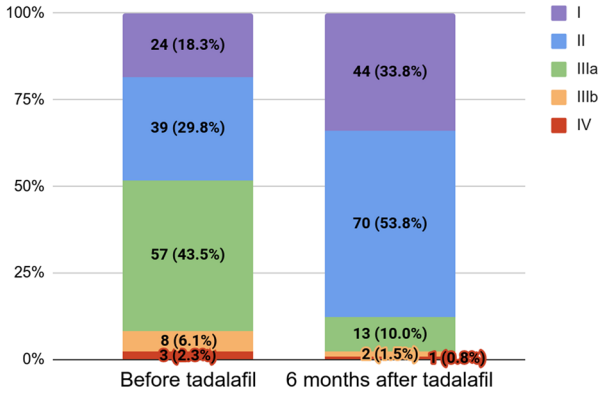

FIGURE 2
WHO functional class before ($n = 131$) and six months after ($n = 130$) tadalafil initiation.

The latter were given lower doses (0.25–0.50 mg/kg) for one–seven days depending on side effect tolerability and inpatient status. Doses were then increased every two–three days (to 1.0 mg/kg for patients under 25 kg, 20.0 mg for patients between 25 kg and 40 kg, and 40.0 mg for patients over 40 kg). The maximum dose utilized was 40.0 mg once daily. Patients who were transitioned from sildenafil to tadalafil had a direct conversion to a full 1.0 mg/kg daily dose (up to a maximum dose of 40.0 mg once daily) that replaced the next dose of sildenafil. Sildenafil was subsequently discontinued.

Table 2 describes the cohort's indications for a tadalafil suspension, tadalafil dosing, prior treatment with sildenafil, and additional therapies. At initiation, the median dose of tadalafil

TABLE 2 Patient medication, summarized as median (minimum–maximum), median (Q_1, Q_3), or count (%).

Variable/level	Summary
Tadalafil dosing	
Initial dose (mg/kg)	1.0 (0.3–1.3)
Maximum dose[a] (mg/kg)	1.0 (0.5–1.0)
Time to maximum dose[a] (days)	1.0 (0.0–766.0)
Indication for tadalafil suspension[b]	
Age (unable to take oral tablets)	103 (66.9%)
Tube fed (gastric or jejunal tube feeds)	49 (31.8%)
Prior sildenafil treatment[b]	
Prior sildenafil duration (days)	30.0 (3.0, 192.5)
Additional vasodilator medical therapy[b]	
Ambrisentan	16 (10.4%)
Bosentan	26 (16.9%)
Macitentan	1 (0.6%)

[a]The values of Q_1 and Q_3 for these variables are all 1.0 mg/kg or 1.0 days, with the exception of time to maximum dose, which has $Q_3 = 2.0$ days.
[b]At tadalafil initiation.

was 1.0 (range 0.3–1.3) mg/kg once daily. About two-thirds of patients required a tadalafil suspension due an inability to swallow tablets (stemming from age). The median duration of sildenafil therapy prior to tadalafil was 30.0 ($Q_1 = 3.0$, $Q_3 = 192.5$) days. At initiation, 26 (16.9%) patients were additionally being treated with bosentan, 16 (10.4%) with ambrisentan, and 1 (0.6%) with macitentan.

Of the few adverse treatment effects reported before initiation, reflux was noted in 4 patients (2.6%), flushing or rashes in 2 (1.3%), and other side effects in 5 (3.2%) (namely, desaturation and ventilation/perfusion mismatch, hair thinning/loss, pulmonary edema, and urinary incontinence). After six months of tadalafil therapy, only 2 (1.3%) patients reported side effects (specifically, reflux) and 146 (94.8%) patients reported no significant adverse effects. No obvious differences in side effects between the transition and *de novo* groups (notably, with respect to hypotension, dizziness, and gastrointestinal symptoms) were observed. See **Table 3** for a summary of adverse effects at both time points.

Effects of tadalafil on echocardiographic measures and biochemistry

Changes in echocardiographic parameters from baseline (prior to tadalafil) to six months after initiation are summarized in **Table 4**. Median right-ventricular systolic pressure (RVSP) decreased over the six-month period from 50.5 ($Q_1 = 35.0$, $Q_3 = 64.0$) mmHg to 37.0 ($Q_1 = 30.0$, $Q_3 = 48.5$) mmHg. There was no appreciable change in median mean pulmonary arterial pressure (mPAP) from 15.3 ($Q_1 = 6.1$, $Q_3 = 29.5$) mmHg to 17.0 ($Q_1 = 10.0$, $Q_3 = 33.0$) mmHg. Although we observed a slight improvement in right-ventricular fractional area change (RVFAC) from 35.0% ($Q_1 = 30.3\%$, $Q_3 = 42.8\%$) to 37.1% ($Q_1 = 31.0\%$, $Q_3 = 44.0\%$), the median change per patient was negative at −0.9 ($Q_1 = -5.3$, $Q_3 = 8.0$) mmHg. Median tricuspid annular plane systolic excursion (TAPSE) improved slightly from 1.1 ($Q_1 = 0.8$, $Q_3 = 1.6$) cm to 1.3 ($Q_1 = 1.1$, $Q_3 = 1.7$) cm and median eccentricity index decreased slightly from 1.3 ($Q_1 = 1.1$, $Q_3 = 1.7$) to 1.2 ($Q_1 = 1.0$, $Q_3 = 1.4$). Of these changes, only those for RVSP and TAPSE were statistically significant ($p \leq 0.003$).

Atrial septal defects (ASDs) were present in 77 (50.0%) patients at baseline: of these, 44 had a left-to-right shunt and 25 had a bidirectional shunt. At six months, 60 (39.0%) patients had an ASD: among these, 38 had a left-to-right shunt and 16 had a bidirectional shunt. Ventricular septal defects (VSDs) were present in 26 (16.9%) patients at baseline: of these, 17 had left-to-right shunts and 6 had bidirectional shunts. Following six months of therapy, 23 (14.9%) patients had a VSD: among these, 15 had a left-to-right shunt and 5 had a bidirectional shunt.

Table 5 summarizes biochemical measures for the cohort. We observed a statistically significant change ($p = 0.001$) in median NT-proBNP levels from 659.0 ($Q_1 = 217.0$, $Q_3 = 2261.0$) ng/L to 346.0 ($Q_1 = 194.5$, $Q_3 = 1125.8$) ng/L from baseline to six months after initiation. Statistically significant changes in other biochemical measures (e.g., hemoglobin, urea, creatinine, aspartate transaminase, and alanine transaminase) were not detected ($p \geq 0.064$).

TABLE 3 Adverse effects of treatment before and six months after tadalafil initiation, summarized as count (%).

Side effect	Before tadalafil	Six months after tadalafil
Dermatological[a]	2 (1.3%)	0 (0.0%)
Ears, nose, and throat	0 (0.0%)	0 (0.0%)
Gastrointestinal[b]	4 (2.6%)	2 (1.3%)
Hypotension	0 (0.0%)	0 (0.0%)
Neurological	1 (0.6%)	0 (0.0%)
Other[c]	5 (3.2%)	0 (0.0%)
None	143 (92.9%)	146 (94.8%)

[a]Dermatological adverse effects (before tadalafil) included one case of flushing and one case of rashing.
[b]Gastrointestinal adverse effects consisted entirely of reflux (gagging or retching).
[c]Other symptoms included frequent desaturation and ventilation/perfusion mismatch, hair thinning/loss, pulmonary edema, and urinary incontinence. One "other" symptom was not reported.

Mortality

In our cohort of 154 patients, there were a total of 8 (5.2%) deaths in the six months following initiation. Of these deaths, 5 were male. The patients who died were aged 0–15 years. None of the deaths were directly related to tadalafil and none featured severe side effects. Two patients had progressive severe pulmonary vein stenosis (PVS) with an element of precapillary PH and were initiated on the tadalafil suspension and followed closely. Three patients had progressive ventricular dysfunction and were not candidates for heart or lung transplants (1 severe left-ventricular diastolic dysfunction, 1 failing Glenn, 1 failing Fontan); these patients remained on tadalafil for symptom improvement. Neither the patients with progressive ventricular dysfunction nor the PVS patients had significant pulmonary edema secondary to Tadalafil. Two patients had severe developmental lung disease (1 bronchopulmonary dysplasia, 1 alveolar capillary dysplasia). Both of these patients were too severe to survive to a transplant work-up/listing and died despite additional aggressive PAH therapy. One patient received tadalafil for severe idiopathic PAH in a liquid formulation while intubated and died following a lung transplant from severe end-organ dysfunction; this patient was off liquid tadalafil following the transplant. All patients in this group tolerated the suspension formulation of tadalafil. All were intubated and required a liquid formulation as a method of administration *via* a feeding tube, including the older patients.

Comparisons between PH groups

Supplementary Tables S2–S4 present comparisons of hemodynamic and echocardiographic parameters, biochemistry levels, and adverse effects between the patients in groups 1, 3, and 5. In comparing echocardiographic parameters, we focus on groups 1 and 3 here since these parameters cannot be meaningfully interpreted for complex single-ventricle patients. There were no significant

TABLE 4 Echocardiographic measures before and six months after tadalafil initiation, summarized as median (Q_1, Q_3) or count (%).

Variable/level	Before tadalafil	Six months after tadalafil	Difference[a]
Echocardiographic parameters			
Eccentricity index	1.3 (1.1, 1.7)	1.2 (1.0, 1.4)	−1.0 (−0.4, 0.1) [$p = 0.083$]
mPAP (mmHg)	15.3 (6.1, 29.5)	17.0 (10.0, 33.0)	0.5 (−1.3, 2.0) [$p = 0.953$]
RV/LV	1.0 (0.8, 1.3)	0.7 (0.6, 1.0)	−0.2 (−0.5, 0.1) [$p = 0.064$]
RVFAC (%)	35.0 (30.3, 42.8)	37.1 (31.0, 44.0)	−0.9 (−5.3, 8.0) [$p = 0.929$]
RVSP (mmHg)	50.5 (35.0, 64.0)	37.0 (30.0, 48.5)	−8.0 (−20.0, 0.8) [$p = 0.003$]
TAPSE (cm)	1.1 (0.8, 1.6)	1.3 (1.1, 1.7)	0.3 (0.0, 0.5) [$p = 0.001$]
Atrial septal defect shunt			
Presence of shunt	77 (50.0%)	60 (39.0%)	
Shunt direction: left to right	44 (28.6%)	38 (24.7%)	
Shunt direction: right to left	4 (2.6%)	4 (2.6%)	
Shunt direction: bidirectional	25 (16.2%)	16 (10.4%)	
Shunt gradient (mmHg)	2.3 (1.8, 7.4)	3.9 (1.6, 4.9)	0.0 (−2.3, 0.0)
Ventricular septal defect shunt			
Presence of shunt	26 (16.9%)	23 (14.9%)	
Shunt direction: left to right	17 (11.0%)	15 (9.7%)	
Shunt direction: right to left	3 (1.9%)	2 (1.3%)	
Shunt direction: bidirectional	6 (3.9%)	5 (3.2%)	
Shunt gradient (mmHg)	36.0 (33.0, 39.0)	36.0 (28.5, 42.5)	5.0 (3.0, 7.5)

Note. RV/LV, right–left ventricle diameter ratio.
[a]The Difference column reports paired pre–post differences: $n = 12$ for mPAP, $n \leq 7$ for the shunt gradients, and $n \geq 45$ for all other variables. Formal testing is omitted for both shunt gradients due to the small sample size.

TABLE 5 Biochemical measures before and Six months after tadalafil, summarized as median (Q_1, Q_3).

Variable	Before tadalafil	Six months after tadalafil	Difference[a]
ALT (units/L)	21.0 (17.0, 34.5)	21.5 (15.3, 34.8)	−2.0 (−9.0, 6.0) [$p = 0.241$]
AST (units/L)	37.0 (28.0, 48.8)	36.5 (27.0, 47.8)	−2.0 (−14.3, 6.0) [$p = 0.083$]
Creatinine (umol/L)	27.0 (21.0, 35.0)	24.0 (20.0, 33.0)	−1.0 (−6.0, 4.0) [$p = 0.240$]
Hgb (g/L)	127.0 (112.5, 140.0)	126.0 (113.3, 135.8)	−1.0 (−18.5, 10.5) [$p = 0.330$]
NT-proBNP (ng/L)	659.0 (217.0, 2261.0)	346.0 (194.5, 1125.8)	−372.0 (−1408.0, 31.5) [$p = 0.001$]
Total bilirubin (umol/L)	9.0 (6.3, 16.0)	8.0 (5.0, 12.0)	−2.0 (−7.0, 2.0) [$p = 0.064$]
Urea (mmol/L)	5.0 (3.7, 7.0)	4.0 (3.0, 6.1)	−0.2 (−2.0, 1.2) [$p = 0.330$]
WBC (10^9/L)	8.9 (7.0, 11.6)	8.2 (6.6, 11.3)	−0.3 (−3.8, 1.4) [$p = 0.360$]

Note. AST, aspartate transaminase; ALT, alanine transaminase; Hgb, hemoglobin; NT-proBNP, N-terminal pro B-natriuretic peptide; WBC, white blood cell count.
[a]The Difference column reports paired pre–post differences as median (Q_1, Q_3) [p-value]: $n \geq 77$ for all variables.

differences detected in pre–post changes between the groups. We observed clinically significant differences in NT-proBNP between groups 1 and 3 both before and six months after tadalafil initiation. The median NP-proNBP among group 1 patients was 659.0 ($Q_1 = 199.0$, $Q_3 = 2464.0$) ng/L at baseline and 255.0 ($Q_1 = 136.0$, $Q_3 = 975.0$) ng/L after six months. For group 3 patients, this was 426.0 ($Q_1 = 217.0$, $Q_3 = 1481.5$) ng/L at baseline and 381.0 ($Q_1 = 199.0$, $Q_3 = 915.0$) ng/L after six months.

Discussion

The role of PDE5 inhibitors

The lack of randomized clinical trials in the context of pediatric PAH has led to a dependence on consensus statements and recommendations when managing children with the condition (8). Previous systematic reviews have highlighted the relatively small

number of randomized controlled trials using PDE5 inhibitors such as tadalafil to treat pediatric patients with PAH (8). Despite the beneficial effects of this therapy in improving oxygenation, hemodynamics, and exercise capacity (1–5, 8), some centers have not transitioned from multiple to once-daily PDE5 inhibitor dosing. This may be due to center preference and further driven by a lack of multicenter data and experience, particularly with pediatric patients. For this reason, we presented our experience regarding the safety and tolerability of once-daily enteral tadalafil dosing and the process of transitioning from sildenafil to tadalafil.

There exists a growing body of evidence supporting the use of dual therapy to treat PAH (where PDE5 inhibitors play a crucial role), either alone or in combination treatment strategies (9). Consensus statements have reiterated the importance of PDE5 inhibitors in treating pediatric patients at any stage (10). Although early pediatric guidelines and the literature focused on sildenafil, suspensions for this drug administered thrice daily have the potential to contribute to poor compliance and missed doses in the pediatric population (10–12). The relative ease of administering a tadalafil suspension enterally (e.g., for the 31.8% of patients in the present study who required tube feeding or for infants with comorbidities) along with its long, 90-day shelf life (6) reduces the risk of inaccurate dosing on the part of caregivers and physicians.

Tadalafil transition and dosing

The preference of the two institutions in this study is for patients established on a thrice-daily 1.0 mg/kg dose of sildenafil to be transitioned to a once-daily 1.0 mg/kg dose of tadalafil. The tadalafil suspension used at the centers in this study has been described in other studies (6). We have found this suspension to be stable, palatable, and able to be stored for prolonged periods of time. Future work should consider starting tadalafil *de novo* in neonates and children and target doses of 1.0 mg/kg once daily.

All previous single-center descriptive experiences with tadalafil in the pediatric population (2–4, 13) included patients on sildenafil for at least six months prior to a transition to tadalafil. Our work uniquely highlighted the possibility of a prompt transition from thrice-daily sildenafil to once-daily tadalafil. In our cohort, the median time to transition from full-dose sildenafil to the tadalafil equivalent was one day. Among the 154 patients, 11 (7.1%) were treated with tadalafil *de novo*, i.e., with no prior transition.

Safety and clinical changes

A previous review of the efficacy and safety of PDE5 inhibitor therapy examined the potential adverse effects of tadalafil (13). This prospective, open-label study included 25 patients between the ages of 0.2 and 5.0 years who were initially treated with 1.0 mg/kg of tadalafil once daily. Six of the 25 patients were previously treated with sildenafil. The authors reported that 3 (12.0%) patients experienced headaches and flushing, but that tadalafil was otherwise well tolerated by the cohort (13). In the present study, the safety and tolerability of the therapy was evident as only a few patients experienced adverse effects. At baseline, 4 (2.6%) patients had gastrointestinal side effects, 2 (1.3%) had either flushing or rashes, and 1 (0.6%) had neurological side effects. Six months after initiation, however, only 2 (1.3%) patients reported adverse effects (namely, gastrointestinal). All adverse effects were manageable with non-pharmacological means (e.g., a change in the time of administration or medicating with meals). The patients who started tadalafil *de novo* did not have any adverse effects, which is promising as an initial result. No patients required hospitalization or a discontinuation of therapy. We hypothesize that differences in the adverse effects reported in this study relative to previous works can be attributed to our tendency to establish infants and neonates on a thrice-daily 1.0 mg/kg dose of sildenafil prior to transitioning to a once-daily 1.0 mg/kg dose of tadalafil.

Over the study period, we observed clinical improvements in hemodynamic, biochemical, and echocardiographic measures and statistically significant changes in NT-proBNP levels, RVFAC, and TAPSE. These changes were consistent with the observed changes in WHO FC. However, given the large number of patients in groups 1 and 3, improvements may have been expected and might not be directly correlated to tadalafil usage, especially in comparison to historical therapies such as sildenafil.

In early experiences, the immature glucuronidation pathways of the neonatal and infant populations seemed to contraindicate tadalafil (10). However, pharmacokinetic-based modeling for children under two years of age has established that once-daily tadalafil is safe and efficacious in the pediatric PAH population (9, 14). The current work, even with its small number of *de novo* patients, highlighted the potential for future treatment strategies for pediatric PAH.

Since the 2018 World Symposium on Pulmonary Hypertension, single-ventricle patients with cavopulmonary anastomosis have been reclassified into group 5 (15). This is in addition to a growing population of complex single-ventricle patients who are palliated to Fontan circulation. In this cohort, patients with group 5 pulmonary hypertensive vascular disease (PHVD) made up a startling 21.4% of the patients receiving liquid tadalafil. This study was neither designed nor powered to look more closely at this group of complex patients. We recognize the limited literature on how PDE5 inhibitors should be used in this population. Based on the present study, liquid tadalafil appears to be a feasible, well-tolerated medication for single-ventricle patients meeting the criteria for PHVD.

Comparisons between groups 1, 3, and 5

While the focus of this paper was predominantly on the tolerance and safety of a tadalafil suspension for pediatric PH patients, we also compared patients across groups 1, 3, and 5. Our inclusion of pediatric PH patients in these three groups also makes the current study unique. Some previous studies on tadalafil therapy were limited to group 1 patients (3, 4, 13) the current research does not have this restriction and thus presents a broader look at tadalafil as a treatment for pediatric PAH and highlights the general tolerability of this therapy.

Side effects–including commonly reported ones such as gastrointestinal disturbances, congestion, and hypotension–were rare in these groups after six months of tadalafil (**Supplementary Table S2**). This may be due to the large number of patients who were already established on sildenafil prior to transitioning to the

tadalafil suspension or it may be that many of the side effects occurred initially but resolved with time. While median RVFAC decreased overall, this may be due to differences in measurement, as has been reported in the literature (16). Group 3 patients showed clinical improvements in terms of eccentricity index, right–left ventricle diameter ratio, RVFAC, RVSP, and TAPSE (**Supplementary Table S3**). Since many of these patients have PH associated with bronchopulmonary disease and would have grown significantly over the six-month period, the observed increase in mPAP (to normal levels of under 20.0 mmHg) might have been expected.

In comparing changes in biochemistry across the three groups (**Supplementary Table S4**), prior to starting suspension tadalafil and six months after therapy, the majority of the markers would be related to side effects, of which liver, kidney and bone marrow changes were not clinically significant. NT-proBNP in both groups 1 and 3 saw a clinically significant decline to normal levels after six months of the tadalafil suspension. For the group 1 patients where tadalafil was targeting the pulmonary arterial bed, this improvement is expected since many of these patients have postoperative-associated PAH. Among group 3 patients, for whom the literature is still evolving with respect to the role of pulmonary vasodilators, it is encouraging to see an improvement in NT-proBNP that coincides with clinical improvement. It is impossible to know whether pulmonary vascular bed growth over time or the tadalafil suspension had a larger impact on this biochemical marker. More research is needed in this area.

Among group 5 patients, who were largely complex single-ventricle patients following Fontan palliative surgery, it was not surprising to see a trend toward increasing values of NT-proBNP. It is often struggling single-ventricle patients who are considered for pulmonary vasodilator therapy—first for PDE5 inhibitors. However, it is not known whether the management of PHVD has an effect on outcomes in this population or if PHVD management is a marker of a poor prognosis. More research needs to be done specifically in this growing group of patients to determine an approach to pulmonary vasodilator therapy that includes the use of tadalafil.

Limitations

The present work has a number of limitations. First, while it would be ideal to have data from right-heart catheterization and additional data from magnetic resonance imaging, this is not practical given the age of the patients and the need for anesthesia. We have instead used noninvasive bedside measurements. Second, WHO FC as an instrument for measuring response to therapy has not been validated among infants and children. Similarly, the six-minute walk test, while appropriate in studies of adults, is not applicable or reproducible within the current cohort. Future work examining the long-term pharmacokinetics of PDE5 inhibitors such as tadalafil is necessary as relevant data in the present study is lacking.

Conclusion

Our descriptive analysis of a heterogeneous group of PH patients highlights the tolerability and safety of tadalafil suspensions for infants and children six years of age and under. Tadalafil suspensions administered once daily have a safe and efficacious medication profile for pediatric PH patients. We observed clinically significant medium-term improvements in clinical, echocardiographic, and laboratory parameters among pediatric PH patients treated with a tadalafil suspension, both alone and in combination with other treatments.

Data availability statement

The datasets presented in this article are not readily available due to ethics restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Health Research Ethics Board at the University of Alberta (approval number Pro00120489) and the Institutional Review Board at Children's Wisconsin (approval number 1704191-3). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

All authors have read and approved the final manuscript. DY, SR, CS, KT, and SH were responsible for study screening and data extraction. MP was responsible for data analysis and copy editing. DY, AB, SH, and EK were responsible for writing the manuscript. AB, EK, and SH were responsible for checking and reviewing the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1055131/full#supplementary-material.

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EDITED BY
Martin Koestenberger,
Medical University of Graz, Austria

REVIEWED BY
Paul Critser,
Heart Institute, Cincinnati Children's Hospital Medical Center, United States
Mary Mullen,
Harvard Medical School, United States

*CORRESPONDENCE
Angela Bates
✉ abates@ualberta.ca

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A Canadian, retrospective, multicenter experience with selexipag for a heterogeneous group of pediatric pulmonary hypertension patients

David Youssef[1], Susan Richards[1], Sabine Lague[2], Catherine Sheppard[1], Jenna Smith[3], Erika Vorhies[4], Martin Hosking[5], Matthew Pietrosanu[6] and Angela Bates[1,7]*

[1]Department of Pediatric Pulmonary Hypertension, Stollery Children's Hospital, Edmonton, AB, Canada, [2]Department of Pediatrics, BC Children's Hospital, Vancouver, BC, Canada, [3]Department of Pharmacy, Stollery Children's Hospital, Edmonton, AB, Canada, [4]Department of Pediatric Cardiology, Alberta Children's Hospital, Calgary, AB, Canada, [5]Department of Pediatric Cardiology, BC Children's Hospital, Vancouver, BC, Canada, [6]Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB, Canada, [7]Division of Pediatric Critical Care, Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

Introduction: Selexipag, an oral nonprostanoid prostaglandin receptor agonist, has led to reduced morbidity and mortality in adults with pulmonary arterial hypertension (PAH). While the adult literature has been extrapolated to suggest selexipag as an oral treatment for severe pediatric pulmonary hypertension (PH), longitudinal, multicenter data on the benefits of selexipag in this population are lacking. The purpose of this study is to present a longitudinal, multicentre experience with selexipag in a relatively large cohort of pediatric PH patients and add to the existing selexipag literature.

Materials and methods: We performed a retrospective, multicenter review describing the clinical outcomes of pediatric PH patients receiving selexipag in addition to standard oral pulmonary vasodilator therapy across three Canadian centers between January 2005 and June 2021.

Results: Twenty-four pediatric patients (fifteen female) with a mean age of 9.7 (range 2.0–15.5) years were included. Of this cohort, eighteen (75.0%) were in group 1, one (4.2%) was in group 2, four (16.7%) were in group 3, and one (4.2%) was in group 4. Twenty-two (91.7%) patients were on dual PH therapy after six months. Dosing was targeted to achieve 20–30 mcg/kg/dose orally every twelve hours. Median dose after twelve months was 30 mcg/kg/dose. Twelve months following selexipag initiation, median decreases of 0.2 cm in tricuspid annular plane systolic excursion, 3.5 mmHg in right-ventricular systolic pressure, and 6.1 mmHg in mean pulmonary arterial pressure were observed; none of these changes were statistically significant. Three patients died, one clinically deteriorated and required admission to a pediatric intensive care unit, ten had gastrointestinal symptoms, and three had flushing.

Conclusion: Selexipag appears to be a safe and effective adjunctive therapy for pediatric PH patients and has a tolerable adverse effect profile aside from gastrointestinal disturbances. Additional prospective studies of changes in hemodynamics and functional classification over a longer period and with a larger sample are needed. Future research should aim to identify subgroups that stand to benefit from the addition of selexipag as well as optimal timing and dosing for the pediatric population.

KEYWORDS

adverse effect, congenital heart disease, echocardiography, infant, nonprostanoid, prostaglandin receptor, side effect

1. Introduction

Pulmonary hypertension (PH) is a rare disorder with a high burden of morbidity and mortality. Estimates of incidence and prevalence are comparable across registries around the world despite their slightly different inclusion and diagnostic criteria. Historical data from two large pediatric registries (United States and Europe) suggest a PH incidence of 4–10 cases per million children per year and a prevalence of 20–40 cases per million children among the pediatric population (1). Mortality is particularly high for patients with idiopathic or heritable pulmonary arterial hypertension (PAH). Without appropriate treatment or a lung transplant, PAH is a progressive and fatal chronic disease. As such, improving patient quality of life and decreasing the risk of mortality through pulmonary vasodilators has proven key to the chronic management of pediatric PH.

Understanding of the pathophysiology of pediatric PH has grown significantly over the past decade. Collaborative efforts, most recently in 2018 through the 6th World Symposium on Pulmonary Hypertension (WSPH), have refined classification groups using evolving knowledge of this disease in the pediatric population (2, 3). The two dominant groups of pediatric PH according to this system are group 1, which includes patients with the disease at the pulmonary arterial level, and group 3, which encompasses patients with an underlying lung pathology. Along with classification systems, knowledge of hemodynamics is evolving, most notably regarding the group 1 category of the disease (**Supplementary Table S1**). Pulmonary vasodilators have historically been targeted at group 1 patients. However, an evolving body of experience suggests that a subset of group 3 pediatric patients benefit from these same vasodilator therapies (2–4).

Given the heterogeneity and complex etiology of pediatric PH, there is a need to expand the existing body of literature on treatment options and outcomes with combination therapy. Although extrapolation from robust adult data has driven the use of various agents to treat pediatric PH, there are major differences between adult and pediatric PH. These include characteristic differences in etiology, presenting symptoms, and acute vasodilator response (3, 4). Children with PH not only have different pathophysiologies, but also tend to have more-aggressive PH than their adult counterparts as well as unique pharmacokinetic and developmental factors. Treatment strategies for pediatric PH must take these differences into consideration.

Current treatment options for pediatric PH, as for adult PH, aim to target one of three major pathways: the endothelin, nitric oxide, and prostacyclin pathways (5, 6). Oral ERA and PDE5 inhibitor therapies respectively target the endothelin and nitric oxide pathways. Synthetic prostacyclins, which target the prostacyclin pathway, are administered either subcutaneously, orally, by inhalation, or by central venous lines (CVLs). In particular, CVL catheter care presents significant challenges for both patients and caregivers, requires sterile procedures, and is associated with higher risks of infection and thrombosis, which further contributes to the morbidity and mortality of pediatric PH (7). The availability and use of subcutaneous treprostinil, a prostacyclin therapy that has improved mortality among pediatric patients in group 1 and has benefits similar to epoprostenol, has lowered the risks associated with CVLs, slowed disease progression, and improved clinical outcomes. However, dermatitis and site pain are very common adverse effects of subcutaneous treprostinil (8).

Sitbon et al. (9) reported that triple-upfront, PH-targeted therapy benefits adult patients with severe PH; their multicenter, double-blind, placebo-controlled phase 3 study showed that, for group 1 adults, selexipag significantly decreases complications and death related to PH. Although oral and inhaled forms of prostacyclin were available in other regions, until selexipag, an oral nonprostanoid prostaglandin receptor agonist, was approved by Health Canada in January 2016, in Canada, treatments acting on the prostacyclin pathway required continuous subcutaneous or intravenous infusion. The addition of an oral prostaglandin receptor agonist was a welcome addition in the early management of aggressive adult PH, but until recently its utility in the pediatric population was limited to regions or countries with access. Within Canada, both out of necessity and availability, the use of selexipag across pediatric PH groups is growing. This oral option offers more-aggressive therapy earlier in the course of the disease and significantly improves patient quality of life. However, given the lack of evidence in this particularly vulnerable population, clinical conditions and the course of the disease need to be followed closely.

Despite the growing collective experience with selexipag for treating pediatric PH (10–14), present literature on the clinical benefits of this drug is scarce, especially with regards to the younger population (**Supplementary Table S1**). The largest study of pediatric PH is a multicenter case report series from Germany that describes experiences with selexipag in patients with WHO functional classifications of III and IV. Most other data on the benefits and side effects of selexipag come from a small number of case reports. No multicenter research on selexipag outcomes in the pediatric population exists in the present literature.

The purpose of this study is to examine the clinical outcomes of pediatric patients with PH who receive selexipag therapy in addition to standard pulmonary vasodilator therapy. We anticipate that selexipag is a beneficial adjunctive therapy for pediatric PH and can help improve quality of life and clinical measures.

2. Materials and methods

We present a retrospective study of pediatric patients with PH who were prescribed selexipag therapy. We characterized clinical progression while on selexipag through close clinical follow-ups, biochemical markers, echocardiographic examinations, cardiac catheterization hemodynamics, the six-minute walk test, dosing patterns, and drug tolerance.

Patients between 0 and 18 years of age with a PH diagnosis who were managed at one of three participating pediatric PH centers in Western Canadian and who had been prescribed selexipag by their PH specialists were included. Data from the Stollery Children's Hospital, Alberta Children's Hospital, and BC Children's Hospital between January 1, 2005 and June 30, 2021 were used in this study.

Assessments were performed at baseline, selexipag initiation, and six and twelve months after initiation. Demographic and clinical data were collected for all patients at baseline. Anthropometric data, cardiac catheterization data, echocardiographic data, and clinical measures were collected at each time point.

This work was approved by the Health Research Ethics Board at the University of Alberta (approval number Pro00084720).

Statistical analyses were conducted using R version 3.6.3 (15). We present descriptive statistics to summarize patient demographics and clinical characteristics at each time point. Comparisons between baseline and twelve months are conducted with paired Wilcoxon signed-rank tests with a threshold significance of 0.05. Raw p-values (i.e., without adjustment) are presented throughout.

3. Results

Of the twenty-four patients included in this study, fifteen (62.5%) were female. The median age at initiation was 9.7 (range 2.0–15.5) years. Eighteen (75.0%) patients were in group 1, one (4.2%) was in group 2 (4.2%), four (16.7%) were in group 3, and one (4.2%) was in group 4. Among all patients, seventeen (70.8%) had underlying congenital heart disease (CHD) and five (20.8%) had obstructive sleep apnea. Trisomy 21 was present in four (16.7%) patients and DiGeorge syndrome in one (4.2%). Comorbidities varied among the patients: two (8.3%) were preterm infants, three (12.5%) had underlying respiratory diseases, five (20.8%) had ENT issues, two (8.3%) had musculoskeletal issues, and one (4.2%) had neurological issues. Summaries of these and other demographic and clinical characteristics are provided in **Table 1**; see **Supplementary Table S2** for more-detailed comorbidity classifications. At the initiation of therapy, median patient weight was 28.4 ($Q_1 = 24.4$, $Q_3 = 37.7$) kg and median height was 136.0 ($Q_1 = 112.9$, $Q_3 = 149.6$) cm. Anthropometric data over the course of the study period are summarized in **Supplementary Table S3**.

Despite initial improvements, three patients died. One of these patients was in group 2 with a background of critical aortic stenosis and underwent balloon valvuloplasty, but showed evidence of endocardial fibroelastosis. This patient ultimately received a left-ventricular assistance device, fared well on oral selexipag, but died from complications secondary to a HeartMate III pump exchange. The second patient was suspected to have capillary hemangiomatosis, but died from an underlying immune deficiency and chronic interstitial lung disease. The third patient, who was born prematurely and had trisomy 21, had a complete atrioventricular septal defect and Eisenmenger physiology, and died from a secondary viral infection prior to prostacyclin therapy.

Supplementary Table S4 summarizes changes in the therapies received by the cohort. At twelve months, twenty-two (91.7%) patients were on dual pulmonary vasodilator therapy. At baseline, all patients were established on selexipag at 200 mcg twice per day, with dose increments every two–four days by 200 mcg/dose until the maximum achievable dose. We found dosing to be in line with the adult literature at 20–30 mcg/kg every twelve hours. At twelve months, the median maximum dose was 30.0 ($Q_1 = 26.0$, $Q_3 = 36.5$) mcg/kg/dose. The maximal therapy was based on previous adult literature (16), the GRIPHON study (9), and early pediatric data (**Supplementary Table S1**). If a patient developed side effects prior to achieving the target maximum dose, no further dose increases were implemented.

Additional therapy in the form of bilevel positive pressure ventilation (BiPAP) was required by four (16.7%) patients at twelve months. Twelve (50.0%) patients required oxygen therapy

TABLE 1 Demographic and clinical characteristics at baseline and comorbidities at selexipag initiation, presented as median (Q_1, Q_3) or count (%).

Variable/level	Summary
Demographics	
Sex: female	15 (62.5%)
Sex: male	9 (37.5%)
Age (years)	9.7 (7.5, 11.0)
WSPH classification (code) at diagnosis	
Idiopathic PAH (1.1)	8 (33.3%)
BMPR2 mutation (1.2.1)	1 (4.2%)
PAH associated with congenital heart disease (1.4.4)	9 (37.5%)
PH due to left heart disease (2)	1 (4.2%)
PAH due to lung disease (3)	4 (16.7%)
PAH due to chronic pulmonary artery obstruction (4)	1 (4.2%)
Comorbidities[1]	
Asthma	1 (4.2%)
Clotting disorder	2 (8.3%)
Congenital heart disease	17 (70.8%)
Obstructive sleep apnea	5 (20.8%)
Other	14 (58.3%)
None	1 (4.2%)
Genetic syndromes	
DiGeorge syndrome	1 (4.2%)
Noonan syndrome	0 (0.0%)
Russell–Silver syndrome	0 (0.0%)
Trisomy 21	4 (16.7%)
Other	2 (8.3%)

[1]Refer to Supplementary Table S2 for a further breakdown.

at twelve months. By the end of the study period, thirteen (54.2%) patients were on diuretic therapy and four (16.7%) required anticoagulant therapy. Over the study period, there was a reduction in the number of patients on prostacyclin therapy from eleven (45.8%) at baseline to three (12.5%) at twelve months as a third agent. Intravenous/subcutaneous remodulin was the preferred agent. Failing patients were placed back on intravenous/subcutaneous remodulin. Oral and inhaled prostacyclin was not used in the population. Gastrointestinal disturbances were reported in ten (41.7%) patients, cardiovascular adverse effects in three (12.5%), and dry lips or rashing in two (8.3%). Two (8.3%) patients experienced neurological symptoms, namely, headache and mood alteration. See **Supplementary Table S5** for a detailed breakdown of adverse effects. Over the course of the study, one patient was delisted for a lung transplant due to disease progression and was kept on triple therapy. This patient survived.

Table 2 summarizes clinical and echocardiographic assessments as well as WHO functional classifications (WHO FCs) for the cohort at initiation, six months, and twelve months. The distribution of WHO FC at these time points is visualized in **Figure 1**. We did not detect statistically significant changes in echocardiographic measures between selexipag initiation and twelve months, although median decreases in tricuspid annular plane systolic excursion (TAPSE), right-ventricular systolic pressure (RVSP), and mean pulmonary arterial pressure (mPAP) were observed. A statistically significant change in six-minute walk test distance (6MWD) was not detected despite an observed increase. Statistically significant changes in WHO FC between initiation and twelve months were not detected: in our cohort, four (16.7%) patients improved with respect to WHO FC, while fifteen (62.5%) had no change and five (20.8%) saw an increase in WHO FC (i.e., a progression of symptoms) over this period.

Supplementary Table S6 summarizes hemodynamic cardiac catheterization data collected at all four time points. This data is sparse, with measures from at most four patients available at any point, so no formal comparisons were conducted and we do not discuss these results in detail here. In short, we observed median increases in all measures under three different conditions (room conditions with 21% FiO_2, 100% O_2, and 100% O_2 with 20 ppm inhaled NO).

4. Discussion

4.1. Role of selexipag in treating pediatric PH

While PH is currently a progressive and fatal disease, the treatment landscape is changing rapidly. The delivery of multimodal pharmacotherapy that interacts with different pathways has changed treatment strategies and the clinical course

TABLE 2 Clinical and echocardiographic imaging measures and wHO FC, presented as median (Q_1, Q_3) and count (%), respectively.

Measure	Initiation	6 months	12 months	Comparison[1]
Echocardiographic measures				
Eccentricity index	1.5 (1.2, 2.0)	1.4 (1.1, 1.8)	1.3 (1.1, 1.6)	0.0 (-0.3, 0.1) [0.48]
mPAP (mmHg)	40.0 (27.4, 46.6)	20.5 (8.0, 44.5)	24.0 (15.5, 38.0)	-6.1 (-8.7, -3.0) [0.09]
RV/LV	1.0 (0.7, 1.6)	1.1 (0.9, 1.4)	1.1 (1.0, 1.6)	0.0 (-0.1, 0.3) [0.63]
RVFAC (%)	34.0 (28.0, 38.0)	34.5 (31.0, 40.0)	36.0 (29.6, 40.5)	0.0 (-2.0, 10.0) [0.67]
RVSP (mmHg)	73.0 (56.5, 92.5)	58.0 (51.0, 85.0)	64.0 (50.5, 70.0)	-3.5 (-12.5, 16.4) [0.95]
TAPSE (cm)	1.9 (1.6, 2.3)	2.1 (1.5, 2.5)	1.5 (1.2, 1.8)	-0.2 (-0.4, 0.2) [0.17]
TR velocity (cm/s)	387.0 (312.0, 488.6)	280.0 (5.0, 423.0)	302.4 (32.2, 369.1)	-9.6 (-45.7, 0.0) [0.07]
Six-minute walk test				
Total distance walked (m)	483.5 (401.8, 571.2)	528.0 (499.0, 619.5)	605.0 (476.2, 623.2)	71.5 (-38.0, 250.0) [0.44]
Pre SaO_2 (%)	97.0 (91.0, 98.0)	97.0 (95.0, 97.5)	96.0 (94.0, 97.0)	0.0 (-2.5, 1.5) [0.83]
Post SaO_2 (%)	90.0 (79.0, 93.0)	90.0 (89.0, 90.5)	95.0 (85.0, 97.0)	4.0 (-3.0, 6.0) [0.81]
WHO FC				
Class I	3 (12.5%)	4 (16.7%)	4 (16.7%)	0.0 (0.0, 0.0) [1.00]
Class II	13 (54.2%)	15 (62.5%)	11 (45.8%)	
Class III	8 (33.3%)	5 (20.8%)	9 (37.5%)	

Note. In all summaries, $n \geq 13$ (but $n = 9$ for mPAP and $n = 24$ for WHO functional classification).
Note. RV/LV, ratio of right to left ventricle diameter; RVFAC, right-valve fractional area change; TR, tricuspid regurgitation.
[1]The Comparison column presents paired differences between initiation and twelve months as median (Q_1, Q_3) [p-value]. P-values are computed using paired Wilcoxon signed rank tests and are unadjusted. In all tests, $n \geq 12$ (but $n = 6$ for total distance walked and mPAP, $n = 7$ for pre SaO_2, and $n = 5$ for post SaO_2).

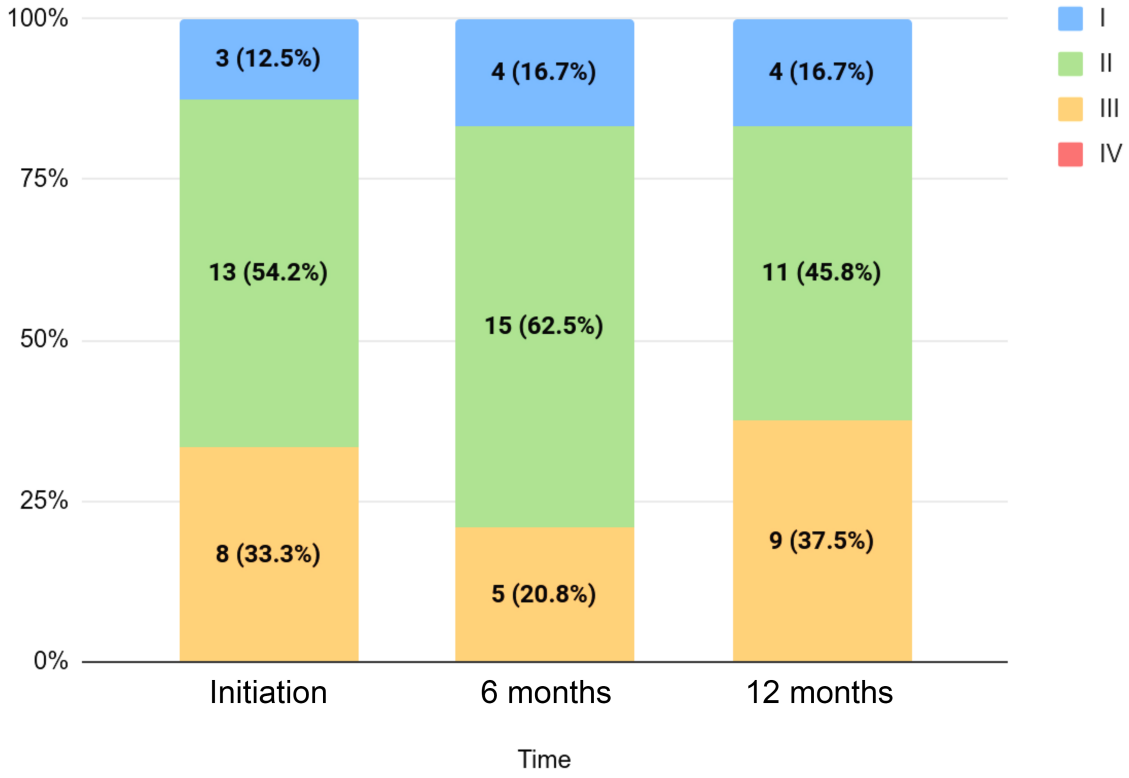

FIGURE 1
WHO functional class for the cohort at initiation, six months, and twelve months.

of the disease for many children. Selexipag offers physicians the opportunity to escalate treatment for severe pediatric PAH patients without the challenges associated with central access, compliance to inhalation therapy, or the pain of subcutaneous therapy (site-related or dermatitis). The problem of patient selection aside, it is difficult to ensure that pediatric patients are on equivalent or optimal doses of therapy to prevent disease progression or clinical worsening while minimizing adverse effects.

We recognize that identifying pediatric PH patients who would be most responsive to selexipag therapy is difficult with either noninvasive (e.g., echocardiography) or invasive (e.g., cardiac catheterization) tools. Responses from individual patients are difficult to establish without a trial period. It would be ideal to add selexipag therapy to treatment regimens both prior to disease progression and when patients are most clinically responsive to selexipag: this can only be achieved through a better understanding of the relationship between selexipag's pharmacokinetic and pharmacodynamic properties in the pediatric population. In our current work it is evident that there are specific patients for whom the addition of selexipag therapy to dual combination therapy was beneficial. On a larger scale, timing selexipag therapy for pediatric PH patients requires multicenter collaborations to identify patients likely to respond to selexipag therapy prior to disease progression or deterioration.

4.2. Clinical response to selexipag

Overall, we observed improvements in WHO FC, 6MWD, right–left ventricle (RV/LV)diameter ratio, mPAP, and TAPSE, although none of these changes were statistically significant. A prospective study by Hansmann et al. (17) with fifteen patients (age 7 months–17 years) on selexipag observed improvements in mPAP, right-ventricular systolic function, and functional classifications as well as pediatric PH prognostic risk scores that trended toward lower serum NT-proBNP concentrations. In their cohort, three patients showed disease progression and two ultimately received a lung transplant. The authors reported that the efficacy of selexipag was variable but often saw better responses in "less-sick patients".

Parameters such as WHO FC, RV/LV diameter ratio, and TAPSE have been used as surrogates for transplant-free survival. In the pediatric population, these clinical and imaging parameters assess response to treatment and guide treatment modifications (18). We observed statistically nonsignificant improvements in cardiac catheterization measures, echocardiographic parameters, and clinical outcomes (including WHO FC and 6MWD). In nineteen (79.2%) patients we observed a constant or improved WHO FC over the twelve-month study period. While attempts were made in our cohort to measure serial laboratory parameters, not all patients had their

serial NT-proBNP levels drawn. We postulate that clinical improvements in WHO FC and 6MWD are correlated with improvements in NT-proBNP levels and that the former can be used as a treatment response indicator. Research by Hansmann et al. (17) noted that those most likely to respond to selexipag might not all have the same disease severity despite worsening clinical symptoms. Hence, there is a poor correlation between individual disease severity and response to selexipag therapy. Change in individual patients needs to be further delineated to determine criteria for ideal candidates and the optimal timing for initiating therapy.

While an adverse effect profile can be rate-limiting for many clinicians when considering dose or treatment escalation, we chose to gradually optimize doses based on individual patient tolerance and the adverse effects experienced by our cohort (16). Despite slow dose increases, a total of ten (41.7%) patients reported gastrointestinal adverse effects (namely, abdominal pain, decreased appetite, diarrhea, and nausea), three (12.5%) reported cardiac adverse effects (namely, flushing), two (8.3%) reported neurological adverse effects, and two (8.3%) reported dermatological adverse effects. With the exception of one patient who required admission to a pediatric intensive care unit, the patients were managed conservatively and without the need to cease therapy. The tolerability of adverse effects is an imperative consideration when treating pediatric PAH in order to reduce noncompliance and disease progression. Our work suggests that the adverse effects of selexipag are tolerable for patients within the range of the clinical, echocardiographic, and catheterization parameters and at the dose described.

4.3. Selexipag for PAH-associated CHD

The early experience of Koestenberger and Hansmann (19) regarding patients with idiopathic PAH and PAH-CHD highlighted the threefold benefit of adding selexipag to standard dual (PDE5 inhibitor and ERA) therapy: it avoids CVL insertion for children and teenagers, helps stabilize the disease, and acts as a bridge to lung transplant. Even when underlying CHD is managed with shunt closure, aggressive therapy for underlying PAH is required to negate the impact of PAH on the pulmonary vascular bed. This is particularly relevant in our study, where seventeen (63.0%) patients had underlying CHD, of whom ten had PAH-CHD. Further research is needed to delineate the role of selexipag in the treatment and management of PAH-CHD and pediatric PH.

The proportion of patients who later develop PAH differs between those with simple and complex CHD (17, 19, 20). Approximately 3% of patients with simple lesions with a small defect (e.g., ventricular septal defects) will develop irreversible damage (i.e., Eisenmenger syndrome) if left untreated. It appears that patients with either simple or complex lesions (the latter nearly always associated with irreversible damage) stand to benefit when selexipag is added to their treatment regimen. Future work can explore the benefits of oral prostanoid therapy for simple or complex CHD and potential reductions in the impact of late-development PAH. Long-term, multicenter pediatric studies are required to better understand the impact of selexipag on PAH-CHD and the utility of this therapy in managing PAH related to simple and complex cardiac lesions.

4.4. Dosing, transition strategy, and adverse effects of selexipag

Dosing in PH therapy in general, let al.one with selexipag, has always presented a challenge: the difficulty lies in determining optimal dose targets and in timing therapies as current pediatric dosing is based on the adult literature. For selexipag, this is a maximum of 1,600 mcg twice per day or until prostacyclin-managed side effects cannot be managed (16). Even in the adult population, dosing is not clear: the median dose in the FREEDOM-M trial following twelve weeks of gradual increases was 3,400 mcg twice daily with a comment that the "maintenance dose is determined by tolerability" (17, 20). As previously mentioned, other works (16) have proposed a maximum dose of 1,600 mcg twice daily with the caveat that the maximum dose should be tailored to the tolerability of adverse effects. In our multicenter study, all participants were titrated to twice-daily doses of 20–30 mcg/kg/dose as per the adult literature. Most patients who weighed more than 45 kg maxed out at twice-daily doses of 1,400 mcg due to side effects, similar to what is described in the adult experience. Our study was not designed to determine the pharmacokinetics of selexipag in a heterogeneous group of PAH patients. As such, more collaborative work is needed to determine optimal dosing for patients with pediatric PAH.

The dosing regimen employed in this work adhered to the following points.

- Children weighing under 20 kg were started on a twice-daily, 100 mcg regimen, with increases of 100 mcg/dose every week up to a target dose of 30 mcg/kg twice daily.
- Children weighing more than 20 kg were started at 200 mcg twice daily with increases of 200 mcg/dose each week to a target dose of 30 mcg/kg twice daily with a maximum dose of 1,600 mcg twice daily.

Kanaan et al. (21) implemented a different dosing schedule with two-thirds of their cohort on a median dose of 2,000 mcg/dose three times daily. This regimen may have been implemented to facilitate the transition from intravenous or subcutaneous treprostinil therapy to enteral selexipag and may account for the adverse effects noted in their cohort. Hansmann et al. (17) implemented dosing similar to that in our study that aimed for a final dose of 30 mcg/kg/dose twice daily. The jaw and neck pain reported in the GRIPHON study (by 17%–26% of patients) was not found in our cohort over the study period: this could be related to the medical interpretation of reports from children. The most frequently reported adverse effects in our cohort were gastrointestinal: three patients had abdominal pain, three had decreased appetite, three had diarrhea, and one had nausea. Side

effects were managed conservatively and no patients ceased therapy secondary to these effects.

4.4.1. Transition strategy

Transitions from intravenous or subcutaneous treprostinil were performed over the course of four–seven days in hospital by titrating down treprostinil with each dose of selexipag and generally escalating each dose by 100–200 mcg depending on patient weight (100 mcg increases for patients under 20 kg and 200 mcg increases for patients over 20 kg) to a goal of 30 mcg/kg/dose twice per day or a maximum of 1,600 mcg twice daily (although as above, most patients were stopped at a twice-daily, 1,400 mcg dose due to side effects). If patients experienced adverse effects from excessive vasodilator side effects (e.g., headache, flushing, dizziness, low blood pressure), the selexipag dose was held constant for one or two titrations down on remodulin. Most titrations of remodulin were in 2.5–5.0 ng/kg/min increments. The site was generally kept running low-dose normal saline for 24 h after achieving the target selexipag dose to ensure that a re-initiation of remodulin was not necessary. All but one transition was performed in hospital. One home transition was performed with weekly titrations following a similar pattern.

The difference in adverse effects reported by adults and children can likely be explained at the cellular level. In addition to metabolic differences, there are characteristic differences in receptor numbers and density between adults and children (22). Through the action of prostanoid receptors on the endogenous prostacyclin pathway, variability in the number of receptors and their responsiveness may account for differences in the frequency and number of adverse effects reported by adults and children as well as differences in treatment efficacy between these populations. However, there is currently no way to use prostacyclin receptor numbers to characterize patients with a robust or minimal response to selexipag.

Additionally, predisposing genetic syndromes in the pediatric population need to be considered: up to 34% of individuals with Down syndrome and PH are known to have gastroesophageal reflux disease and thus a possible predisposition to gastrointestinal upsets and aspiration (23). Further exploration of optimal dosing, pharmacokinetics, and pharmacodynamics in pediatric PAH is necessary to minimize adverse effects and maximize drug efficacy (19, 23).

4.5. Patient selection

One common theme in our experience is the lack of a clear selection procedure to identify subgroups of pediatric PH patients that would benefit most from the addition of selexipag and the disease stage at which an oral agent acting on the prostacyclin pathway would be most effective. We utilized selexipag therapy in three broad groups. The first included patients who were slowly improving (with respect to WHO FC, hemodynamics, and 6MWD) and prostacyclin naïve ($n = 5$). The second contained patients further along in the course of the disease who improved on intravenous or subcutaneous prostacyclin therapy but wanted to try an oral agent for quality-of-life reasons ($n = 11$). The third group contained a small subset of patients for which selexipag was introduced on compassionate grounds where intravenous or subcutaneous prostacyclin was not an option: this was most commonly for behavioral reasons and a family's or caregiver's strong belief, after weighing respective risks and benefits, that an oral medication was favorable ($n = 8$). In these cases, doses were occasionally pushed higher than the standard 20–30 mcg/kg/dose in the twice-daily regime.

The lack of knowledge on whether selexipag has the same benefits as traditional prostacyclin in terms of remodeling with antiproliferation and antiplatelet action presents another significant challenge. This therapy is still in its infancy for the pediatric population, so this question will remain unanswered until more long-term data is collected.

4.6. Limitations

We recognize that our multicenter data is retrospective and dependent on chart reviews of a small (but, relative to previous works, notable) number of pediatric PAH patients. We are not able to comment on long-term follow-up for these patients given the cohort's heterogeneity, the death of three patients, and the need for one patient to be listed for lung transplant. While we observed patients who benefited from selexipag therapy, we also observed patients with no change despite treatment with maximally tolerable therapy. Further collaborative work to determine criteria for identifying ideal candidates (i.e., those who respond to early selexipag therapy) is required. Additionally, our study cohort did not have biochemical data (e.g., serial measurements of NT-proBNP) available for all patients as surveillance protocols differed between the three centers.

5. Conclusion

Selexipag, an oral prostanoid with an active metabolite, offers clinicians a promising therapeutic option for escalating treatment in pediatric patients with severe PH without the challenges associated with other current therapies. In this work, we presented a multicenter experience with this therapy in a heterogeneous group of pediatric PAH patients. A number of patients benefited from the addition of selexipag to standard dual (PDE5 inhibitor and ERA) therapy. Statistically significant changes in echocardiographic parameters, hemodynamic measures, and WHO FC were not detected over the twelve-month study period, although we observed improved or constant WHO FCs for nineteen (79.2%) patients. Nonetheless, we argue that this therapy is an invaluable addition to current treatment regimens, especially for patients who are not suitable candidates for intravenous or subcutaneous therapy and who are unlikely to comply with multiday inhalation therapy or for whom disease stabilization is required as a bridge to transplant. The most common adverse effects of this therapy are gastrointestinal in nature. Dosing should reach the current literature's recommendation of 30 mcg/kg/dose

twice per day with adjustments according to adverse effects. Future work should focus on the relationship between selexipag's pharmacokinetics and pharmacodynamics in pediatric PH patients to determine optimal initiation and dosing regimens, maximize adherence, and minimize intolerance.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Materials**. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants in this work were reviewed and approved by the Health Research Ethics Board at the University of Alberta (approval number Pro00084720). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

DY, SR, CS, SL, EV, and MH were responsible for study screening and data extraction. MP was responsible for data analysis and copy editing. DY and AB were responsible for writing the manuscript. EV and MH were responsible for checking and reviewing the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1055158/full#supplementary-material.

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EDITED BY
Angela Bates,
University of Alberta, Canada

REVIEWED BY
Peter Oishi,
University of California, San Francisco, United States
Uri Pollak,
Hadassah Medical Center, Israel

*CORRESPONDENCE
Jenna M. Faircloth
jmfaircl@texaschildrens.org
Neelam D. Bhatt
ndbhatt2@texaschildrens.org

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Case Report: Selexipag in pediatric pulmonary hypertension: Initiation, transition, and titration

Jenna M. Faircloth[1]*, Neelam D. Bhatt[1]*, Corey A. Chartan[2], Ryan D. Coleman[2], Natalie Villafranco[3], Fadel E. Ruiz[3], Raysa Morales-Demori[4], Elise Whalen[5], Erin Ely[5], Rozmeen Fombin[5] and Nidhy P. Varghese[3]

[1]Department of Pharmacy, Texas Children's Hospital, Houston, TX, United States, [2]Department of Pediatrics, Division of Critical Care and Pulmonology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States, [3]Department of Pediatrics, Division of Pulmonology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States, [4]Department of Pediatrics, Division of Critical Care, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States, [5]Department of Pulmonary Medicine, Texas Children's Hospital, Houston, TX, United States

Selexipag, a selective prostacyclin receptor agonist, is approved for treating pulmonary arterial hypertension in WHO Group 1 adult patients. Compared to parenteral prostacyclin formulations, selexipag offers a significant improvement in patient's and caregiver's quality of life because of its oral formulation, frequency of administration, and mechanism of action. Although experience in the pediatric population is limited to case reports in older adolescent patients and selexipag is not approved for use in the pediatric pulmonary hypertension population, many pediatric centers are expanding the use of this therapy to this population. We report our institution's experience in the use of selexipag to treat pulmonary hypertension in children under 10 years of age, between 10 and 30 kg. Seven patients were initiated on selexipag therapy including *de novo* initiation and transition from intravenous treprostinil to oral selexipag. All patients were on stable background therapy with phosphodiesterase-5 inhibitor and endothelin receptor antagonist therapies at baseline. All patients reached their planned goal selexipag dose during admission without the need for changes to the titration schedule and without hemodynamic deterioration. In our experience, oral selexipag is safe and well-tolerated in young pediatric patients with pulmonary hypertension. Based on our favorable experience, we developed an institution-specific selexipag process algorithm for continued successful use in the pediatric population.

KEYWORDS
pediatric pulmonary hypertension, selexipag, treprostinil, initiation, transition, prostacyclin

1. Introduction

Pediatric pulmonary arterial hypertension (PH) is a rare, progressive disease associated with significant morbidity and mortality. Current therapies target three main physiologic pathways: the nitric oxide, endothelin, and prostacyclin pathways. Oral agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic PH in adults include phosphodiesterase-5 inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (bosentan, ambrisentan, macitentan), prostacyclin analogs such as oral treprostinil, and soluble guanylate cyclase stimulators (riociguat). Oral agents are generally preferred by patients and families over parenteral or inhaled therapies due to lower treatment burden and are therefore associated with increased medication adherence. Selexipag, a selective prostacyclin receptor agonist, was approved by the FDA in 2015 as the second oral

prostacyclin pathway-targeted therapy option for adult WHO Group 1 patients. Clinical trials demonstrated a lower incidence of side effects, less frequent dosing, and administration without regard to food compared to oral treprostinil (1). The longer half-life successfully maintained efficacy and reduced side effects in the setting of a missed dose. As with oral treprostinil, avoiding subcutaneous (SQ) or intravenous (IV) access was associated with improved quality of life.

SQ administration of prostacyclins is associated with pain at the SQ site, and central line infections are a common complication with chronic IV access. Central/SQ line care, dressing changes, flushes, travel restrictions and precautions, and limited ability to participate in similar activities as their peers often make parenteral therapy complex and time-consuming. The burden parenteral prostacyclin therapy places on patients, their caregivers, and their families is significant and widespread. Oral selexipag has offered flexibility to caregivers and reduced complications to patients for those who can tolerate it. Response to selexipag therapy and clinical stability are similar to those seen with parenteral prostacyclin in adult studies (2, 3). Given these advantages and pharmacokinetics, selexipag is an attractive therapy choice. Therefore, although experience in the pediatric population is limited primarily to case reports in adolescent patients and selexipag is not approved for use in the pediatric pulmonary hypertension population, many pediatric centers are expanding the use of this therapy to this population (4–8).

However, the safety and efficacy of selexipag have not been established in pediatric patients, nor is selexipag FDA-approved for pediatric use. At the time of manuscript preparation, there is an ongoing randomized, double-blind, placebo-controlled clinical trial of selexipag in pediatric PH patients aged 2–17 years evaluating time to disease progression, with estimated study completion in 2028 (9). As trial results are awaited, it is essential that large center experience is shared to assist in current clinical practice and to identify optimal initiation, transition, and titration of selexipag therapy. There are adult data that can be extrapolated to guide clinical practice; however, pharmacokinetics vary greatly between these two populations; therefore, the framework for selexipag use in pediatrics has to be tailored to this population. Therefore, in this case series, we present our experience in rapid selexipag initiation and transition from parenteral treprostinil in young pediatric PH patients, along with an institution-specific process algorithm, to bridge the gap resulting from the lack of a standardized approach in this population.

2. Methodology

Seven patients were initiated on selexipag therapy. A standardized process was developed for the initiation and rapid transition to selexipag (**Figure 1**). Once candidates for selexipag initiation or transition were identified by the treating physician, medication approval was obtained. The patient was then scheduled for admission to the pediatric intensive care unit (PICU) to begin selexipag in a monitored setting.

Upon admission, throughout the hospital stay, and particularly at discharge, the PH pharmacist and PH physician educated the patient, family, and bedside nursing staff regarding possible adverse effects of titration (hypotension, chest pain, dyspnea, hypoxemia). Using pictorial graphs and medication calendars, education was provided on different tablet strengths, the importance of adherence, and timely administration.

For *de novo* initiation in children <30 kg, selexipag was initiated at 50 µg every 12 h and rapidly titrated up in 50 µg per dose per day increments until the goal dose was achieved, roughly 4 days. To determine the goal dose, we utilized an equivalent of IV treprostinil; 10 ng/kg/min IV treprostinil was equivalent to 100 µg selexipag every 12 h for patients <30 kg and 10 ng/kg/min IV treprostinil was equivalent to 200 µg selexipag every 12 h for patients ≥30 kg. Upon reaching the goal dose, the patient was discharged to continue slower titration in the outpatient setting.

Similarly, to determine selexipag goal dose and titration increments for transitions from IV treprostinil to oral selexipag, we utilized an equivalent of IV treprostinil; 10 ng/kg/min IV treprostinil was equivalent to 100 mcg selexipag every 12 h for patients <30 kg and 10 ng/kg/min IV treprostinil was equivalent to 200 µg selexipag every 12 h for patients ≥30 kg. During the rapid transitions from IV treprostinil, selexipag was administered first and immediately followed by IV treprostinil dose reduction by an increment of 2–5 ng/kg/min per step. Selexipag 200 µg tablets were used to facilitate dose titrations and adjustments. For smaller-dose titration steps and/or patients who could not swallow tablets, 200 µg tablets were dissolved in 4 ml of water to yield a mixture of 50 µg/ml, as described by Koo et al. (4). Dose titrations were directly observed by the inpatient PH team, and every patient was monitored as per PICU protocol.

We present a review of the seven patients who received selexipag therapy from May 2020 to September 2021 at our institution. Each patient case was reviewed for baseline information: age, WHO Group classification, comorbidities, background therapy, weight at the time of selexipag treatment initiation, 6-min walk distance (6 MWD), right ventricular (RV) pressure estimate, and baseline mean pulmonary artery pressure (mPAP) as measured within the past year.

3. Cases

3.1. *De novo* selexipag initiation and titration

3.1.1. Case 1

A 3-year-old boy with WHO Group 1 PAH presented with the worsening disease despite dual-targeted therapy. The mPAP at diagnosis was 36 mmHg. However, 2 years later, when referred to our center, the RV systolic pressure estimate by echocardiogram was at least 61 mmHg. Past medical history was significant for persistent pulmonary hypertension of the newborn and bone marrow transplant in the context of MECOM mutation. Parenteral prostacyclin therapy was recommended but declined by the family due to the perceived treatment burden. Selexipag therapy was therefore agreed upon as an alternative.

At the time of selexipag initiation, the patient weighed 14.6 kg. A baseline 6-min walk test could not be done due to age/developmental status. The baseline echocardiogram estimate of RV pressure was at

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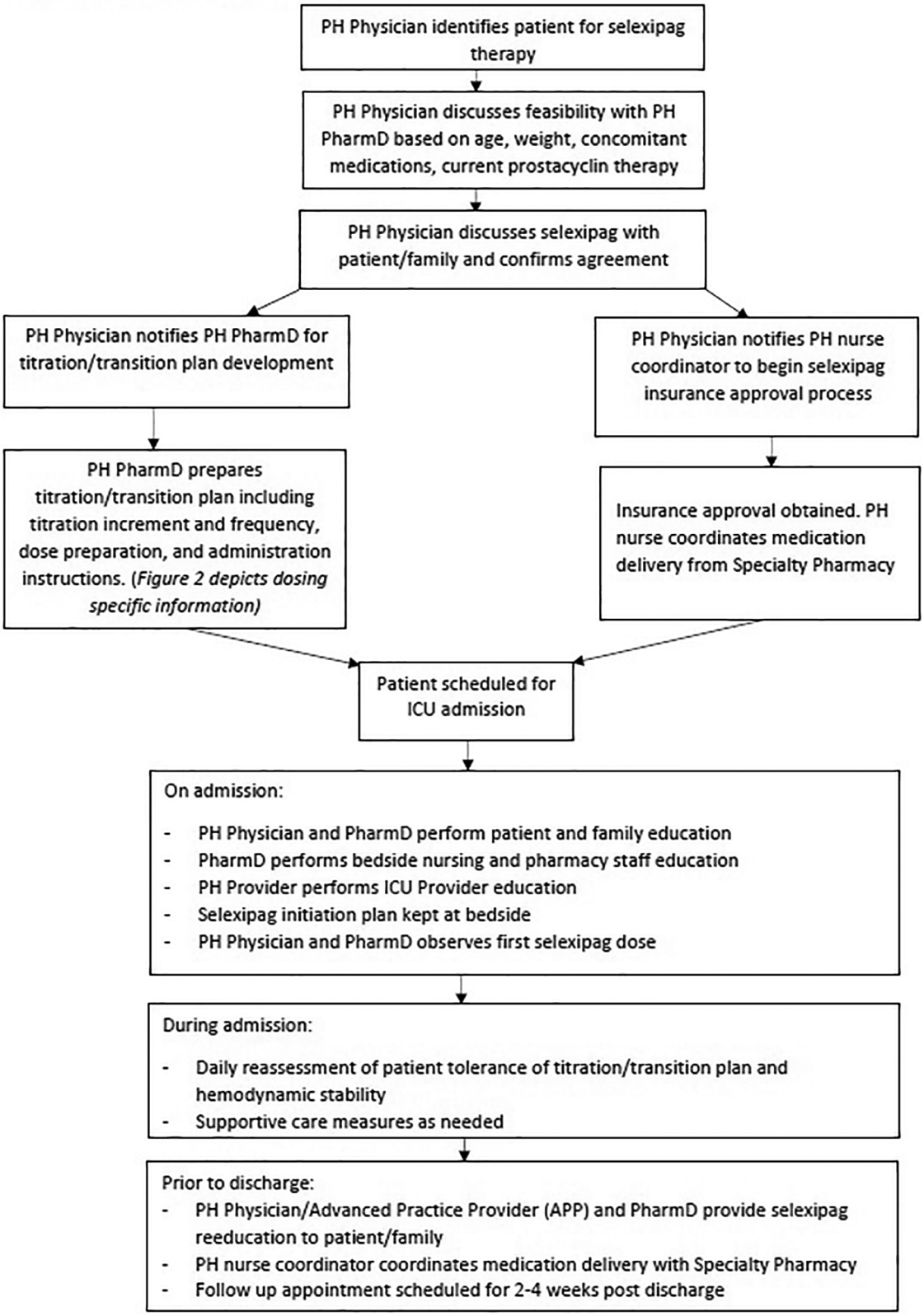

FIGURE 1
Institution-specific selexipag initiation algorithm.

least 70 mmHg. Cardiac catheterization had not been repeated since diagnosis 2 years prior. Selexipag was initiated at 50 μg (1 ml of 200 μg/4 ml solution) every 12 h. Over the course of the next 4 days, selexipag dosing was titrated by 50 μg per dose once daily up to the goal dose of 200 μg every 12 h. The patient tolerated the transition well without significant events. Six months after

initiation, the family reported subjective improvement in activity and endurance. On serial assessments, the child was noted to have increased weight gain and a consistent increase in 6MWD. The echocardiographic estimate of RV systolic pressure was 77 mmHg. Although he was clinically progressing in a positive direction, since his echocardiogram was largely unchanged, the selexipag dose was increased without complication by 100 µg per dose weekly up to 400 µg every 12 h. Functional class improved from class III to class II. Cardiac catheterization was performed 19 months after selexipag initiation, and mean PAP was 56 mmHg, consistent with echocardiograms at that time. Concerns about consistent oral dosing administration and absorption prompted reconsideration of parenteral prostacyclin therapy, so the child was ultimately transitioned successfully from selexipag to IV treprostinil.

3.1.2. Case 2

A 5-year-old girl with trisomy 21 and PH associated with the late repair of atrioventricular septal defect (AVSD) presented with worsening PH. Comorbidities included a history of extracorporeal membrane oxygenation, tracheostomy, gastrostomy tube placement, adrenal insufficiency, factor V Leiden deficiency, and hypothyroidism. Although she had been classified as a Group 1 PAH patient, recurrent aspiration and associated chronic lung disease were suspected, prompting consideration for Group 3 exacerbating diseases. She had been on dual therapy; however, interval catheterization showed elevated PA pressures and indexed pulmonary vascular resistance. Selexipag was selected due to limited caregiver resources to support parenteral prostacyclin therapy in the outpatient setting.

At the time of selexipag initiation, the patient weighed 15.1 kg. The baseline 6-min walk distance was 254 m. The baseline echocardiogram estimate of RV pressure was 44 mmHg. Baseline cardiac catheterization was 53 mmHg before selexipag initiation. Selexipag was initiated at a dose of 50 µg (1 ml of 200 µg/4 ml solution) every 12 h over 4 days. Selexipag dose was titrated by 50 µg per dose each day up to the goal dose of 200 µg every 12 h. Once outpatient, dose titration continued to 250 µg every 12 h. However, with this continued dose titration, the caregiver noted facial flushing, decreased appetite, intermittent diarrhea, and headache, so the dose was decreased back to selexipag 200 µg every 12 h. Six months after initiation, the child's functional status was judged to be improved to class I, and the family reported subjective improvement in activity and endurance. Her 6MWD was improved to 314 m. The echocardiographic estimate of RV systolic pressure was 43 mmHg. Interval cardiac catheterization had not yet been completed (elapsed time since initiation = 12 months) at the time of manuscript submission.

3.2. Parenteral treprostinil to selexipag transition and titration

3.2.1. Case 3

A 5-year-old girl on triple combination therapy to treat severe hereditary PAH (Group 1 secondary to BMPR2+ and KCNA5+ mutations) was evaluated for conversion from IV treprostinil to selexipag due to repeated admissions for central venous line-related complications (damaged line and infections).

At the time of selexipag initiation, the patient weighed 14 kg. The baseline 6-min walk distance was 190 m. The baseline echocardiogram could not estimate RV pressure; however, the septal motion was moderately to severely flattened with associated moderate RV dysfunction. Baseline cardiac catheterization measured mPAP 59 mmHg before selexipag initiation. The patient was started on selexipag 100 µg every 12 h and increased by 100 µg per dose daily while decreasing IV treprostinil by 5 ng/kg/min every 12 h. The transition from IV treprostinil 62 ng/kg/min to selexipag 600 µg every 12 h was completed in 6 days. The transition was well tolerated. Six months after initiation, the child's functional status was judged to be class II. The family reported subjective improvement, and at the time of this study, she has not had any more admissions since conversion to selexipag. Her 6MWD was 292 m at 6 months post-transition. The echocardiographic estimate of RV systolic pressure could not be quantified; however, the septum was noted to be flattened, and RV systolic function was judged normal. Interval cardiac catheterization has not been done due to social barriers affecting scheduling (elapsed time since transition = 23 months).

3.2.2. Case 4

An 8-year-old girl was newly diagnosed with Group 1 PAH after 1 year of worsening dyspnea with exercise, syncopal episodes, and severe right ventricular dysfunction necessitating extracorporeal membrane oxygenation support. Baseline cardiac catheterization data were obtained while on (clamped) extracorporeal support ad epinephrine, vasopressin, and calcium chloride infusions. The mean PA pressure on this support was measured to be 35 mmHg. She was able to come off mechanical support on upfront combination therapy of tadalafil, ambrisentan, and IV treprostinil 36 ng/kg/min. The patient had a surprisingly robust response to therapy, with complete normalization of the echocardiogram. Due to limited resources for the family and the normal echocardiogram, prostacyclin therapy was adjusted from IV treprostinil to selexipag.

At the time of selexipag transition, the patient weighed 30.6 kg. Baseline 6MWD could not be done since the child was still admitted to intensive care and was judged to be too critically ill to participate in testing. A baseline echocardiogram performed on IV treprostinil prior to transition could not quantify the RV pressure estimate; however, septal motion and RV function were normal. She was started on selexipag 100 µg every 12 h. IV treprostinil was decreased by 4 ng/kg/min twice daily immediately after each selexipag dose. Selexipag was increased by 100 µg per dose daily in the morning until a goal dose of 800 µg every 12 h was achieved. She transitioned over 6 days and tolerated the transition well with no side effects. At the 6-month follow-up, the child's functional status was judged to be class I. Her 6MWD at 6 months was 469 m. The echocardiographic estimate of RV systolic pressure was 33 mmHg. Interval cardiac catheterization showed an mPAP of 30 mmHg.

3.2.3. Case 5

An 8-year-old boy with idiopathic PH (due to ABCA3 point mutation), WHO Group 1, on triple therapy with ambrisentan,

tadalafil, and SQ treprostinil dose of 100 ng/kg/min was identified for selexipag therapy to improve quality of life after 6.5 years of SQ therapy. At the time of selexipag initiation, the patient weighed 18 kg. The baseline 6-min walk distance was 391 m. The baseline echocardiogram estimate of RV pressure was 64 mmHg. Baseline cardiac catheterization, done on triple therapy 2 years before transition, measured an mPAP of 26 mmHg. Of note, it had been 35 mmHg on diagnostic catheterization 5 years prior. Selexipag was initiated at 100 mcg every 12 h. Intravenous treprostinil was decreased by 5 ng/kg/min twice daily immediately after every selexipag dose. Selexipag was increased by 100 mcg per dose once daily up to a goal of 600 µg every 12 h over 6 days. The patient tolerated the transition well during the admission. He was discharged 12 h after the last dose change without any adverse events. Selexipag dose was increased outpatient to 1,200 µg every 12 h over the following year. Six months after initiation, the child's functional status was still considered class I, and the family reported great energy levels as demonstrated by the child running laps with other children. His 6 MWD was 566 m. The echocardiographic estimate of RV systolic pressure was 52 mmHg. Interval cardiac catheterization 9 months after transition showed an mPAP of 29 mmHg.

3.2.4. Case 6

A 10-year-old boy with PH, WHO Group 1, on triple therapy with ambrisentan, tadalafil, and IV treprostinil 128 ng/kg/min, was identified for selexipag therapy. The treatment plan was tailored to encourage remodeling for the ultimate closure of a patent ductus arteriosus (PDA); however, cardiac catheterization data did not support intervention. Unfortunately, lung transplantation was not a good option because of the preserved right ventricular function. Therefore, in consideration for quality of life given the unlikely consideration for ductal closure, conversion from IV treprostinil to selexipag was offered.

At the time of selexipag initiation, the patient weighed 23 kg. His baseline 6MWD was 547 m. The baseline echocardiogram showed a bidirectional shunt across the PDA. Baseline cardiac catheterization measured an mPAP of 52 mmHg before selexipag transition. He was on IV treprostinil 128 ng/kg/min, which was weaned down weekly outpatient to 100 ng/kg/min, with regular echocardiographic monitoring. The reason to decrease the treprostinil dose outpatient prior to transitioning to selexipag was to decrease overall hospital stay and start selexipag at a dose that fits within the approved adult dosing recommendation (i.e., <1,600 µg twice daily.) When he reached the target IV treprostinil dose of 100 ng/kg/min, he was admitted and started on selexipag 100 µg every 12 h. Treprostinil was decreased by 5 ng/kg/min twice daily immediately after every selexipag dose. Selexipag was increased by 100 mcg per dose once daily up to a target dose of 1,000 µg every 12 h over 10 days. He was discharged 24 h after the last dose change. He had no side effects during admission, and his upper and lower extremity oxygen saturations were noted to be matched. Selexipag was increased outpatient to 1,200 µg every 12 h to address frequent leg cramps and tiring; however, he had increased side effects (nausea, stomach pain, and headache) with a morning dose of selexipag. This was treated with more consistent meals, ondansetron pretreatment, and oxygen supplementation during meals. As side effects improved, his dose was increased over 2 months to 1,600 µg every 12 h outpatient. After reaching the maximum dose, he reported a good energy level and fewer foot desaturations. Six months after initiation, the child's functional status was class II. His 6MWD was 577 m. Echocardiograms continued to demonstrate the bidirectional shunt (unchanged) at the PDA. Interval cardiac catheterization showed an mPAP of 51 mmHg.

3.2.5. Case 7

A 2-year-old boy patient with repaired D-transposition of the great arteries who was subsequently palliated with reverse Potts shunt procedure for continued severe disease presented for conversion from SQ treprostinil to selexipag in the post-Potts shunt period. The postoperative period was unremarkable; however, the child experienced frequent site changes and skin reactions to the subcutaneous dressing, so he was transitioned to selexipag. At the time of selexipag initiation, the patient weighed 10.5 kg. The baseline 6-min walk distance could not be done due to age and mobility. The baseline echocardiogram showed a bidirectional shunt at the level of the reverse Potts shunt. Baseline cardiac catheterization measured an mPAP of 76 mmHg before selexipag titration. The patient started titration at a dose of 50 µg selexipag (1 ml of 200 µg/4 ml solution) every 12 h. In contrast to the other treprostinil to selexipag transition patients, 2 ng/kg/min treprostinil steps were selected due to the patient's previous history of sensitivity with dose escalation of prostacyclin, during SQ treprostinil initiation. Treprostinil was decreased by 2 ng/kg/min twice daily immediately after every selexipag dose. Selexipag was increased by 50 mcg per dose once daily to a goal dose of 200 mcg every 12 h over 5 days. He tolerated the transition well, with no side effects. He was discharged 12 h after the last dose change. As an outpatient, he was transitioned to tadalafil, and the selexipag dose was increased to 600 mcg every 12 h over 4 months. Six months after initiation, the child's functional status continued to be class I. The family reported matched upper and lower extremity saturations. The child was noted to have consistent weight gain. At the time of this study, he remained developmentally too young for 6MWD. Echocardiograms were stable on selexipag, demonstrating the bidirectional shunt across the reverse Potts shunt. Interval cardiac catheterization was not sought post-transition (elapsed time = 15 months).

3.3. Clinical characteristics of patients

Patient demographics prior to selexipag therapy are displayed in **Table 1**. Seven patients were initiated on selexipag therapy. Two (29%) patients had *de novo* initiation, and five (71%) patients were transitioned on admission from intravenous treprostinil to oral selexipag. Four of seven (57%) patients were boys. Four of seven (57%) patients were 5 years old or younger. All patients were WHO Group 1 and were on stable background therapy with a PDE5 inhibitor and endothelin receptor antagonist. Selexipag dosing strategies and clinical characteristics before and after selexipag initiation are also represented in **Table 1**.

TABLE 1 Characteristics of selexipag initiation patients.

Pt Case ID	WHO group	Age at initiation (years)	Gender (M/F)	Weight at initiation (kg)	Indications for SEL initiation	Concomitant medications	IV TRE dose at SEL initiation	SEL dose at initiation	SEL dose at hospital discharge	Initiation duration (d)	NYHA FC (pre/post)	6 MWD (m) (pre/post)	BNP ng/m (pre/post)	Mean PAP (mmHg) (pre/post)	PVRi (WUm2) (pre/post)	Trans pulmonary gradient (mmHg) (pre/post)
De novo initiation																
1	1	3	M	14.6	Family refusal of parenteral therapy	Tadalafil, ambrisentan	NA	50 μg BID	200 μg BID	4	III/II	NA/382.5	134/49.7	36/56	8.74/12.6	NA/44
2	1, 3	5	F	15.1	Psychosocial; lack of resources for parenteral prostacyclins	Tadalafil, ambrisentan	NA	50 μg BID	200 μg BID	4	I/I	254.14/314.12	41.3/55	53/NA	11.2/NA	43/NA
Parenteral treprostinil to oral selexipag																
3	1	5	F	14	Central line concerns/ frequent admissions for line infections	Tadalafil, ambrisentan IV TRE	62 ng/kg/min	100 μg BID	600 μg BID	6	II/I	189.3/291	54.6/<10	59/NA	16.9/NA	47/NA
4	1	8	F	30.6	Psychosocial; lack of parenteral prostacyclin resources in home city/state	Tadalafil, ambrisentan, IV TRE	36 ng/kg/min	100 μg BID	800 μg BID	6	IV/I	NA/469.25	45/11	35/NA	8.9/NA	22/NA
5	1, 5	8	M	18	Quality of life	Tadalafil, ambrisentan, SQ TRE	60 ng/kg/min	100 μg BID	600 μg BID	6	II/II	566/600	<10/5	26/29	2.2/3.1	11/14
6	1, 3	10	M	23	Compassion-ate conversion from central line to oral therapy to improve quality of life	Tadalafil, ambrisentan, IV TRE	100 ng/kg/min	100 μg BID	1,000 μg BID	10	II/III	547/576.6	62/N/A	51/51	7.4/9.9	37/43
7	1, 3	2	F	10.5	Central line concerns	Sildenafil, bosentan, SQ TRE	20 ng/kg/min	50 μg BID	200 μg BID	5	III/II	NA	53/110	76/NA	18.8/NA	63/NA

TRE, treprostinil; SEL, selexipag; BID, twice daily, spaced by 12 h; IV, intravenous; 6 MWD, 6-min walk distance; PAP, pulmonary artery pressure.

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4. Discussion

This case series describes our experience with *de novo* initiation and rapid transition from treprostinil to oral selexipag in young pediatric patients aged 2–10 years old. Our experience allowed us to develop an institution-specific algorithm (**Figure 1**) and selexipag dosing manual (**Figure 2**) to help guide our practice in using selexipag in younger patients.

The dosing strategy and transition methodology were developed on principles of dose escalation of parenteral prostacyclin therapy, treprostinil and selexipag pharmacokinetics, and historical experience with transitions from IV to oral treprostinil. The median duration of *de novo* selexipag initiation was 4 days. The median duration of the rapid transition to selexipag was 6 days (5–10 days) as it was dependent on the patient's initial treprostinil dose and goal selexipag dose. Patients were generally ready for discharge by 12 h after receiving the final titration dose and were either discharged the same day or the next day, depending on consideration of hour of the day. All patients in our cohort completed the transition as planned, without unexpected events, adverse side effects, and any deterioration in hemodynamic parameters.

Clinical data to support the nasogastric or gastric feeding tube administration route of selexipag is lacking in this population; however, it was deemed successful based on subjective and objective improvement, supporting absorption, in both of our patients. We used the preparation method described in the 2021 case series by Koo et al. (4) with dosing *via* a nasogastric or gastric feeding tube.

Factors we considered relevant for pediatric selexipag therapy were stable disease (i.e., without worse PH symptoms or disease progression), stable prostacyclin doses, quality of life, and availability of resources to support parenteral prostacyclin therapy. Prior to selexipag, our patients were challenged by SQ site infections, SQ site pain, and central line complications. After the transition to selexipag, patients have remained hemodynamically stable and without disease progression, as documented by echo and 6MWD. We believe selexipag may play a role in reducing overall healthcare costs through reduction in unscheduled admissions as our patients admitted frequently for complications due to IV/SQ treprostinil therapy have not had an unscheduled admission since selexipag. All of our patients and their caregivers reported improvements in quality of life. We suggest that our institution-specific algorithm (**Figure 1**) and dosing guide (**Figure 2**) are new tools that can be used for safe selexipag therapy initiation in pediatric patients with stable disease.

A limitation of our case series is the size of the population. However, while our overall cohort was small, we described a consistent experience in using selexipag across a wide age and weight range. Since September 2021, we have applied this process to 10 more patients, all with the same level of success. It must also be noted that process implementation started in May 2020, during the COVID-19 global pandemic. This impacted our ability to directly monitor these patients closely for follow-up postinitiation in the outpatient setting. Due to clinical and access constraints, there were decreased encounters for in-clinic visits, 6MWD testing,

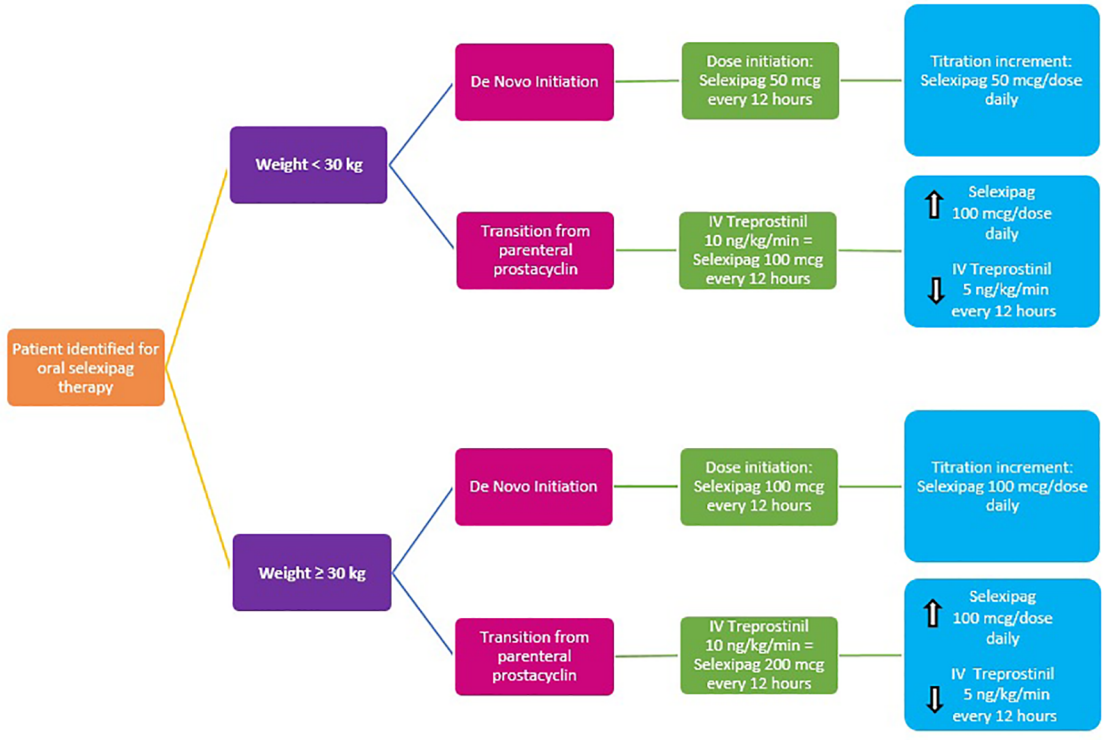

FIGURE 2
Institution-specific selexipag initiation dosing guide.

echocardiography, and cardiac catheterization testing. Therefore, in some instances, follow-up may not be truly long-term or complete.

5. Conclusion

This case series summarizes our center's experience in introducing selexipag therapy in young pediatric patients. Using a process specific to pediatric pharmacokinetics and pharmacodynamics, *de novo* initiation and rapid transition from parenteral treprostinil to selexipag were well-tolerated and safe for children 2–10 years of age and 10–30 kg of body weight. With the support of continuous monitoring in the PICU and thorough education provided by the PH team, medical providers were able to effectively and confidently follow the titrations as planned, and each patient was successfully transitioned home to continue therapy. Follow-up data on selexipag were stable for every patient, without any evidence of clinical worsening. Given this favorable experience and follow-up, selexipag may be a reasonable oral therapy to consider in treating severe but stable pediatric PH. The process algorithm presented can be regarded as a pediatric-specific framework for successful selexipag initiation or transition in this population.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and institutional requirements.

Author contributions

JMF and NDB contributed to conceptualization and methodology. JMF, NDB, CAC, RM-D, RDC, NV, EW, FER, EE, and RF contributed to data collection. JMF, NDB, CAC, RM-D, RDC, NV, EW, and FER contributed to the writing of the original draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Marie-Christine Seghaye,
University Hospital of Liège, Belgium

REVIEWED BY
Hao Zhang,
Shanghai Children's Medical Center, China
Paul Critser,
Cincinnati Children's Hospital Medical Center, United States

*CORRESPONDENCE
Yuxin Fan
✉ Yuxin.fan@bcm.edu

†These authors share last authorship

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Hereditary pulmonary arterial hypertension burden in pediatrics: A single referral center experience

Maki Ishizuka[1], Wenxin Zou[2,3], Elise Whalen[4], Erin Ely[4], Ryan D. Coleman[1], Dolores H. Lopez-Terrada[2,5], Daniel J. Penny[6], Yuxin Fan[7,3*†] and Nidhy P. Varghese[3†]

[1]Department of Pediatrics, Critical Care, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States, [2]Department of Pathology & Immunology, Baylor College of Medicine, Houston, TX, United States, [3]John Welsh Cardiovascular Diagnostic Laboratory, Division of Genomic Medicine, Department of Pathology, Texas Children's Hospital, Houston, TX, United States, [4]Department of Pediatrics, Pulmonology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States, [5]Division of Genomic Medicine, Department of Pathology, Texas Children's Hospital, Houston, TX, United States, [6]Department of Pediatrics, Cardiology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States, [7]Departments of Pathology & Immunology and Pediatrics-Cardiology, Baylor College of Medicine, Houston, TX, United States

Introduction: Hereditary pulmonary arterial hypertension (HPAH) is a rare yet serious type of pulmonary arterial hypertension (PAH). The burden in the pediatric population remains high yet underreported. The objective of this study is to describe the distribution of mutations found on targeted PAH panel testing at a large pediatric referral center.
Methods: Children with PAH panel administered by the John Welsh Cardiovascular Diagnostic Laboratory at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas between October 2012 to August 2021 were included into this study. Medical records were retrospectively reviewed for clinical correlation.
Results: Sixty-six children with PAH underwent PAH genetic testing. Among those, 9 (14%) children were found to have pathogenic mutations, 16 (24%) children with variant of unknown significance and 41 (62%) children with polymorphism (classified as likely benign and benign). BMPR2 mutation was the most common pathogenic mutation, seen in 6 of the 9 children with detected mutations. Hemodynamic studies showed higher pulmonary vascular resistance among those with pathogenic mutations than those without (17.4 vs. 4.6 Wood units). All children with pathogenic mutations had severe PAH requiring triple therapy. There were tendencies for higher lung transplantation rate but lower mortality among those with pathogenic mutations.
Conclusions: Abnormalities on genetic testing are not uncommon among children with PAH, although majority are of unclear significance. However, children with pathogenic mutations tended to present with more severe PAH requiring aggressive medical and surgical therapies. Genetic testing should be routinely considered due to consequences for treatment and prognostic implications. Larger scale population studies and registries are warranted to characterize the burden of HPAH in the pediatric population specifically.

KEYWORDS
pediatrcis, pulmonary arterial hypertension, hereditary, tertiary referral center, genetic

Introduction

Heritable pulmonary arterial hypertension (HPAH) is a rare yet serious type of pulmonary arterial hypertension (PAH). Although adult epidemiologic studies report the median age of diagnosis for PAH is currently in the 3rd–4th decade of life (1, 2), age of diagnosis for HPAH is extremely variable. Emerging clinical and genetic data indicate

that there are fundamental differences between pediatric and adult-onset disease (3, 4), reflecting the influence of epigenetic and possibly environmental factors. There is a greater genetic burden in children with genetic factors contributing to 42% of pediatric onset PAH compared to 13% of adult-onset PAH (3). At present, mutations in 16 genes have been linked to development of HPAH, many of them involved in or affecting the BMPR2 (Bone morphogenetic protein receptor 2) signaling pathway (3, 5). BMPR2 is highly expressed on pulmonary vascular endothelium and mutations in BMPR2 comprise the 70%–80% of HPAH cases (6). The co-factors of BMPR2 endoglin (ENG) and activin receptor like kinase 1 (ACVRL1) are predominantly altered in hereditary hemorrhagic telangiectasia-associated PAH (7, 8). Mutations in the BMP receptor type IA and type 1B [BMPR1A and BMPR1B, also called activin receptor-like kinase 6 (ALK6)], caveolin-1 (CAV1), eukaryotic initiation translation factor 2 alpha kinase 4 (EIF2AK4), potassium two-pore-domain channel subfamily K member 3 (KCNK3), SMAD family members 4 and 9 (SMAD4 and SMAD9), and T-box 4 (TBX4) have all been identified as less frequent or rare causes of PAH (9).

Pediatric PAH differs from adult-onset PAH in many important aspects, including clinical presentation, etiology, genetic burden, and specific genes involved. In pediatric-onset PAH, transcription factors TBX4 and SOX17 are seen with high frequency following BMPR2 (3). TBX4 and SOX 17 are not expressed in pulmonary arterial endothelial cells or smooth muscles, but in embryonic tissues and have prominent roles in lung and vasculature development (10, 11). De novo variants are a frequent characteristic of pediatric-onset PAH, contributing to 15% of patient population (3). These discoveries have prompted considerable development of targeted gene mutation panels for evaluation of pediatric PAH patients. Here we describe the distribution of mutations in a pediatric PAH population of a large referral center.

Materials and methods

Patient population

This was a single center study. Our institution is the largest children's hospital in North America and is also home to the most active pediatric lung transplant program in the country, rendering a diverse and large sample population. Therefore, we retrospectively reviewed the data of children with PAH who had genetic testing at Texas Children's Hospital (TCH) from October 2012 to August 2021. Diagnosis of PAH was made based on echocardiography and right heart catheterization when patients' clinical status allowed.

Genetic testing

The applied PAH gene panel included ACVRL1, BMPR2, CAV1, EIF2AK4, ENG, FLNA, GDF2, KCNA5, KCNK3, NOTCH1, NOTCH3, SMAD4, SMAD8, SOX17 and TOPBP1 genes. This panel was developed and administered by the John Welsh Cardiovascular Diagnostic Laboratory. Specifically, genomic DNA isolated from patient's blood sample was analyzed by sequencing for exons, splice junctions, and flanking regions of all genes tested in this panel. Sequencing analysis was performed by oligonucleotide-based in-solution hybridization target capture (SeqCap EZ, NimbleGen or KAPA HyperChoice, Roche) followed by next generation sequencing (MiSeq, Illumina). Sanger sequencing (3730XL DNA Analyzer, ABI) was used to fill in for gaps/bases that were not sufficiently covered. All clinically significant and novel variants were confirmed by independent Sanger sequencing. DNA sequence was assembled to and analyzed in comparison with the genomic reference sequences (GRCh37/hg19 or GRCh38/hg38) published in the NCBI database to generate variant calls. Variants were annotated through Esembl VEP program, curated *via* AlaMut and open source databases including gnomAD, ClinVar, VarSome and PubMed, and classified according to the ACMG guideline (12). Genetic variations were classified as pathogenic, variant with unknown significance (VUS) and polymorphisms (likely benign and benign). Further/correlating genetic testing was offered to parents as indicated.

Clinical information

Clinical data correlates were obtained by reviewing medical records. Demographic data of the study patients, including age, gender, race, ethnicity, comorbidity and family history of PAH was collected. Clinical information including echocardiography findings, cardiac catheterization results, treatment combinations and outcome were also collected and analyzed. Presence of right ventricular failure was defined qualitatively based on the echo reports. Medical therapy was categorized as monotherapy, dual therapy and triple therapy.

Statistical analysis

Data were analyzed using STATA 13.1 (StataCorp, College Station, TX). Summary statistics were described with mean and standard deviation for parametric variables and median with interquartile range (IQR) for nonparametric variables. Comparison of continuous variables in subgroups was performed using independent t-test or Wilcoxon rank-sum test, one-way analysis of variance, or Kruskal-Wallis depending on normality of distribution. Comparisons of categorical variables between subgroups were analyzed using the Chi-square test. The threshold for statistical significance was p-value <0.05.

Results

There were 66 children with diagnosis of PAH who had genetic testing through John Welsh Laboratory during the study period (**Table 1**). Median (IQR) age of study patients was 4.4 (0.94,

TABLE 1 Demographics of patients by genetic testing results.

Genetic testing	Total ($n = 66$)	Pathogenic ($n = 9$)	Variant of unknown significance ($n = 16$)	Polymorphisms (likely benign and benign) ($n = 41$)
Median age at presentation (years), range	4.4 (0.94, 11.4)	7.6 (4.2, 14.4)	5.6 (1.2, 11.4)	3.0 (0.78, 8.9)
Male, *n* (%)	28 (42)	3 (33)	6 (38)	19 (46)
Race, *n* (%)				
Caucasian	47 (71)	8 (89)	10 (63)	29 (71)
African American	10 (15)	1 (11)	5 (31)	4 (10)
Asian	3 (5)	0 (0)	0 (0)	3 (7)
Other	6 (9)	0 (0)	1 (6)	5 (12)
Hispanic/Latino, *n* (%)	20 (30)	3 (33)	7 (44)	10 (24)
Family history of PAH, *n* (%)	7 (17)	2 (22)	2 (13)	3 (7)
WSPH group, *n* (%)				
Group 1	55 (83)	9 (100)	15 (94)	31 (73)
Group 2	3 (5)	0 (0)	1 (2)	2 (5)
Group 3	14 (21)	0 (0)	3 (5)	11 (27)
Group 4	0 (0)	0 (0)	0 (0)	0 (0)
Group 5	2 (3)	0 (0)	0 (0)	2 (5)
Comorbidities, *n* (%)	40 (61)	4 (44)	8 (50)	28 (68)
Cardiac disease	24 (36)	2 (22)	4 (25)	18 (434)
Pulmonary disease	25 (38)	2 (22)	4 (25)	19 (46)
Hematologic disease	2 (3)	0 (0)	0 (0)	2 (5)
Systemic disease	4 (6)	0 (0)	3 (19)	1 (2)
Metabolic disease	1 (2)	0 (0)	0 (0)	1 (2)

PAH, pulmonary arterial hypertension; WSPH, world symposium of pulmonary hypertension.

11.4) years old. There was female predominance ($n = 38$, 58%). The majority of patients were Caucasian ($n = 47$, 71%) and 19 (40.4%) identified as Hispanic or Latino. The greater part of the study population ($n = 40$, 61%) had comorbidities either in the cardiac or respiratory system. Approximately 10% of children who underwent genetic testing had known family history of PAH.

Nine children (14%) were found to have pathogenic mutations, 16 (24%) with variant of unknown significance and 41 (62%) with –polymorphisms (likely benign or benign) noted. Children with pathogenic mutations older than those without pathogenic mutations. BMPR2 mutation was the most common pathogenic mutation, seen in 6 children (**Table 2**). Other recorded mutations included EIF2AK4 pathogenic mutation, GDF2 pathogenic mutation in one child each respectively. And there was a child who was found to have TBX4 pathogenic mutation later on through a genetic testing out of our lab. The majority of the variants of unknown significance were located in the gene NOTCH1 (38%), followed by NOTCH3 (31%) and KCNA5 (31%).

Eighty-three percent of the study population was classified as World Symposium of Pulmonary Hypertension (WSPH) Group 1, WSPH Group 3 was 21% of patients. Children with features of Group 1 and Group 3 disease were classified in the WSPH group that corresponded to the driver of disease pathogenesis. There were 10 (15%) children who were classified as multifactorial disease (i.e., fit more than 1 WSPH classification), however none of them had pathologic mutations. All children with pathogenic mutations were classified as WHO group 1 (Group 1.2 for

TABLE 2 Identified mutations.

Mutation type, *n* (%)	Pathogenic ($n = 9$)	Variant of unknown significance ($n = 16$)
BMPR2	6 (67) c.1644delC (*p*.Ser549Profs*15) c.186dup (*p*.Gly63Argfs*2) c.2530C > T (*p*.Gln844*) c.189_190insT (*p*.Ser64*) c.1169delG (*p*.Gly390Glufs*3) c.978delA (*p*.Lys326Asnfs*9)	1 (6)
EIF2AK4	1 (11) c.301G > T (*p*.Glu101*) and c.1243delT (*p*.Tyr415Ifs*12)	1 (6)
ACVRL1	0 (0)	0 (0)
ENG	0 (0)	2 (13)
GDF2	1 (11) c.76C > T (*p*.Gln26*)	2 (13)
NOTCH1	0 (0)	6 (38)
NOTCH3	0 (0)	5 (31)
KCNA5	0 (0)	5 (3)
KCNK3	0 (0)	1 (6)
SMAD4	0 (0)	1 (6)
TBX4	1 (11.1) c.1164dup (*p*.Arg389Glnfs*30)	0 (0)
SOX17	0 (0)	1 (6.3)
TOPBP1	0 (0)	1 (6.3)

BMPR2, bone morphogenetic protein receptor 2; EIF2AK4, eukaryotic translation initiation factor 2-alpha kinase 4; ACVRL1, activin receptor like kinase 1; ENG, endoglin; GDF2, growth differentiation factor 2; NOTCH, neurogenic locus notch homolog protein; KCNA and KCNK, potassium channel subfamily A and K; T-box 4, T-box 4; SMAD4, suppressor of mothers against decapentaplegic 4; SOX17, SRY-related high-mobility group box; TOPBP1, DNA topoisomerase II binding protein 1.

HPAH, 1.6 for PVOD). All children with pathogenic mutations had severe PAH requiring triple therapy (Table 3).

On echocardiogram, tricuspid regurgitant (TR) doppler signal was measured in 43 children. Median TR jet was elevated to 5.1 (4.5, 5.6) vs. 4.6 (3.9, 5.2) vs. 4.6 (3.9, 5.0) among children with pathogenic, VUS and polymorphism mutations respectively. The rate of RV failure was the highest in pathogenic mutation group [78% vs. 69% vs. 63%]. Cardiac catheterization revealed the highest pulmonary vascular resistance (PVR) with pathogenic mutations [17.4 (11.1, 26.2) vs. 4.6 (3.9, 5.2) vs. 4.6 (3.9, 5.0)]. About half of the children with pathogenic and VUS mutations had positive vasoreactivity during cardiac catheterization (43%, 50%). Vasoreactivity was least observed among those with polymorphism mutations (29%).

Outcomes for the cohort with identified pathogenic mutation trended to higher rates of transplantation, 33% ($n = 3$) compared to those without pathogenic mutations ($n = 7$, 12%). The age of lung transplantation was similar at 13–15 years old among all genetic groups. The median (IQR) time to the lung transplant was 9.8 (1.2, 72.0) months ranging from 0.78 months to 12.5 years.

Mortality was higher in the non-pathogenic group (VUS and polymorphism composite) compared to the group of patients with pathogenic mutations ($n = 14$, 53% vs. $n = 1$, 11%, $p = 0.53$). The one death in the pathogenic mutation group was a 14 year-old child who died during diagnostic admission; later discovered to have BMPR2 mutation.

Genetic testing was offered to four families with known pathogenic mutation and two families with detected variant of unknown significance. Inherited pathogenic mutations were identified in two families of patients with pathogenic mutation. The first family had a mutation in EIF2AK4. The parents had c.1243delT (*p*.Tyr415Ifs*12) and c.301G > T (*p*.Glu101*) and the child inherited both of these mutations. The second family had a mutation in GDF2: both of the parents had c.76C > T (*p*.Gln26*), which the child inherited. In families with children who resulted with variant of unknown significance, no no pathogenic mutations were identified.

Discussion

We describe the genetic burden of disease within a large pediatric referral center for PH. In our cohort, we identified PAH-associated pathogenic genetic mutations in 13.6% of the patients who otherwise had no obvious etiology for their disease. This is lower than previous studies reporting 20%–50% prevalence of genetic mutations in pediatric onset PAH (3, 13, 14). One of the possible explanations is limitations on our genetic panel not including newer PAH genes such as BMP10, aquaporin 1 (AQP1), ATPase 13A3 (ATP13A3) or kinase insert domain receptor (KDR). BMPR2 mutation was the most common mutation seen among 66.7% of mutations in our population, consistent with the literature. BMPR2 mutation has been reported as the most common mutation in both pediatrics and adults, comprising 6.5%–12.5% of all unexplained pediatric PAH and 36%–65% of pediatric PAH with pathogenic genetic variants (3, 5, 13, 15).

In our patient population, higher TR jet and more RV failure was noted on initial echocardiograms among children with pathogenic mutation, suggesting more clinical burden of disease (16). This trend was confirmed by cardiac catheterization, showing higher PVR among children with pathogenic mutations compared to those without them. PVR among children with pathogenic mutation in our population was similar to the

TABLE 3 Hemodynamic data and clinical outcome of patients by genetic testing results.

Genetic testing	Total ($n = 66$)	Pathogenic ($n = 9$)	Variant of unknown significance ($n = 16$)	Polymorphisms (likely benign and benign) ($n = 41$)	*p*-value*
Echocardiogram, *n* (%)	65/66 (99)	9/9 (100)	16/16 (100)	40/41 (98)	
Tricuspid regurgitant jet (m/sec)	4.6 (4.1, 5.1)	5.1 (4.5, 5.6)	4.6 (3.9, 5.2)	4.6 (3.9, 5.0)	0.22
Presence of right ventricular failure, *n* (%)	43/62 (66)	7/9 (78)	11/16 (69)	25/40 (63)	0.66
Cardiac catheterization, *n* (%)	46/66 (70)	8/9 (89)	13/16 (81)	25/41 (61)	
Pulmonary vascular resistance (Wood units)	4.6 (4.1, 5.1)	17.4 (11.1, 26.2)	4.6 (3.9, 5.2)	4.6 (3.9, 5.0)	0.17
Vasodilation study, *n* (%)	38/46 (81)	7/8 (88)	10/13 (77)	21/41 (51)	
Vasoreactivity, *n* (%)	14/38 (37)	3/7 (43)	5/10 (50)	6/21 (29)	0.48
Transplant, *n* (%)	10 (15)	3 (33)	3 (19)	4 (10)	0.15
Age at transplant (years), median (range)	13.6 (11.9, 15.4)	15.4 (11.8, 15.5)	13.3 (0.97, 13.9)	13.3 (12.3, 14.6)	0.60
Mortality, *n* (%)	15 (23)	1 (11)	5 (31)	9 (22)	0.53
Age at mortality (years), median (range)	11.5 (1.15, 17.0)	14.4 (14.4, 14.4)	11.5 (6.3, 17.0)	4.4 (0.90, 15.8)	0.64
Medical therapy[a], *n* (%)					0.76
None	2 (3)	0 (0)	0 (0)	2 (5)	
Monotherapy	4 (6)	0 (0)	1 (6)	3 (7)	
Dual therapy	7 (11)	0 (0)	2 (13)	5 (12)	
Triple therapy	28 (42)	5 (56)	5 (3)	18 (44)	

[a]Medical therapy excludes children who deceased or received lung transplantation.
**p*-values are for 3 group comparison.

previously reported values of 19.9 WU among children with idiopathic and heritable PAH by Zhang et al. (14). All children with pathologic mutation had severe PAH at presentation and all were started on upfront combination therapy. Outcomes for HPAH in our population were commensurate with reports of severe disease in the literature, including high rate of transplantation. It is interesting to note that the mortality in the HPAH cohort was overall less than the non-HPAH cohort. This may reflect the benefit of upfront aggressive medical treatment that was offered to the group with pathogenic mutation and the expectant referral provided for transplantation in the face of poor prognosis. Although the majority of our population did not have an identified pathogenic mutation on targeted screening, this non-genetic disease group did demonstrate progressive and aggressive disease, consistent with idiopathic PAH, WSPH Group 1 (86%). This percentage is higher than literature reports of 58% idiopathic in the pediatric population (3). This discrepancy may reflect a limitation in our institutional genetic panel or reflect the diversity of our patient population. Advancement in genetic studies including identification of new genetic mutations is required for these patient population.

A previous population-based study among insured United States (US) patients reported that 36% of pediatric PAH patients had a history of prematurity, 75% with congenital heart defect and 13% with trisomy 21 (17). In this selected population that underwent genetic testing, only 8 (12%) children had documented history of prematurity, 18 (27%) had cardiac defect and none of the referred patients had other known PAH associated genetic syndromes such as trisomy 21. This difference is likely reflective of some sample bias as genetic studies were only offered for unexplained or disproportionate PH symptoms.

In addition to the limitations already stated, there was insufficient data on familial testing to report on the benefit of that modality in this study. Although pathogenic mutations were discovered and group classification was changed to WSPH Group 1.2, further familial studies were necessary to confirm hereditary nature of the discovered mutations. Secondly, the overall number of children with pathogenic mutation was small. This is likely a limitation of targeted or known familial mutation testing. Application of broader panels will likely find additional genetic abnormalities. Finally, due to the retrospective nature of the study, our data was limited for data prior to presentation at our center and to testing available during a specific era. Genetic panels are evolving quickly and negative testing in 2012 may not be negative on repeat, expanded testing. The panel that was used for genetic testing in this population was updated over time by adding new genes. Although BMPR2 has been on the panel since testing was started, and this diagnostic yield was not significantly affected over study period, it is possible that mutations in other genes of interest were missed in early testing.

We recognize that the findings in this study may be unique and not be generalizable for the greater pediatric PAH population. However, we hope that this descriptive study informs on the genetic burden of disease in pediatric PH patients and the consideration for genetic screening to affect morbidity and mortality. Certainly, larger population studies and registries for pediatric PAH are warranted to better characterize the greater burden of HPAH and phenotype-genotype correlations.

Conclusion

Genetic mutations are not uncommon among children with PAH. Children affected with pathogenic mutations presented with more severe PAH, higher pulmonary vascular resistance and higher rate of RV failure requiring upfront triple therapy. These children had higher rates of transplantation but improved survival, perhaps because of more aggressive treatment in the setting of known HPAH. Genetic testing should be routinely considered due to consequences for treatment and prognostic implications. Further studies in larger population and registries are warranted to better characterize pediatric HPAH.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.ncbi.nlm.nih.gov/, SCV002575026 - SCV002575059.

Ethics statement

The studies involving human participants were reviewed and approved by Baylor College of Medicine, Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

MI: Generated research idea, collected and analyzed data, developed manuscript. WZ: Performed genetic testing. EW: Collected data and edited manuscript. EE: Collected data. RDC: Collected data. DHL-T: Supervised genetic testing. DJP: Supervised genetic testing. YF: Supervised genetic testing. NPV: Supervised research idea development, collected data and supervised manuscript development. All authors contributed to the article and approved the submitted version.

Conflict of interest

NPV receives research support from the PePH registry.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Catherine Avitabile,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
Trent E. Tipple,
University of Oklahoma Health Sciences Center,
United States
Shazia Bhombal,
Emory University, United States
Randal Buddington,
Louisiana State University Health Shreveport,
United States
Kevin Dysart,
Alfred I. duPont Hospital for Children,
United States

*CORRESPONDENCE
Delphine Yung
✉ dyung2@uw.edu

†These authors have contributed equally to this work and share last authorship

‡PRESENT ADDRESS
Alyssa Blumenfeld,
Division of Neonatology, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, United States

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A multidisciplinary approach to severe bronchopulmonary dysplasia is associated with resolution of pulmonary hypertension

Delphine Yung[1]*, Emma O. Jackson[2], Alyssa Blumenfeld[3‡], Gregory Redding[4], Robert DiGeronimo[5], John K. McGuire[6], Meredith Riker[2], William Tressel[7], Sara Berkelhamer[5†] and Laurie C. Eldredge[4†]

[1]Division of Cardiology, Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, United States, [2]Heart Center, Seattle Children's Hospital, Seattle, WA, United States, [3]Department of Pediatrics, University of Washington, Seattle, WA, United States, [4]Division of Pulmonology, Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, United States, [5]Division of Neonatology, Department of Pediatrics, University of Washington School of Medicine, and Seattle Children's Hospital, Seattle, WA, United States, [6]Division of Critical Care Medicine, Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, United States, [7]Collaborative Health Studies Coordinating Center, Department of Biostatistics, University of Washington, Seattle, WA, United States

Objective: To describe our multidisciplinary bronchopulmonary dysplasia (BPD) consult team's systematic approach to BPD associated pulmonary hypertension (PH), to report our center outcomes, and to evaluate clinical associations with outcomes.
Study design: Retrospective cohort of 60 patients with BPD-PH who were referred to the Seattle Children's Hospital BPD team from 2018 to 2020. Patients with critical congenital heart disease were excluded. Demographics, comorbidities, treatments, closure of hemodynamically relevant intracardiac shunts, and clinical outcomes including time to BPD-PH resolution were reviewed.
Results: Median gestational age of the 60 patients was 25 weeks (IQR: 24–26). 20% were small for gestational age (SGA), 65% were male, and 25% received a tracheostomy. With aggressive cardiopulmonary management including respiratory support optimization, patent ductus arteriosus (PDA) and atrial septal defect (ASD) closure (40% PDA, 5% ASD, 3% both), and limited use of pulmonary vasodilators (8%), all infants demonstrated resolution of PH during the follow-up period, including three (5%) who later died from non-BPD-PH morbidities. Neither SGA status nor the timing of PH diagnosis (<36 vs. ≥36 weeks PMA) impacted the time to BPD-PH resolution in our cohort [median 72 days (IQR 30.5–166.5)].
Conclusion: Our multidisciplinary, systematic approach to BPD-PH management was associated with complete resolution of PH with lower mortality despite less sildenafil use than reported in comparable cohorts. Unique features of our approach included aggressive PDA and ASD device closure and rare initiation of sildenafil only after lack of BPD-PH improvement with respiratory support optimization and diagnostic confirmation by cardiac catheterization.

KEYWORDS

bronchopulmonary dysplasia, pulmonary hypertension, sildenafil, miltidisciplinary care, neonate

1. Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of prematurity and rates are increasing with improved survival of extremely premature infants (1, 2). BPD is defined in infants born at less than 32 weeks gestation as an oxygen and/or respiratory support requirement after 36 weeks postmenstrual age (PMA) (3–6). Pulmonary hypertension (PH) associated with BPD (BPD-PH) is an important comorbidity and 2.7 times more common in infants with severe BPD (7). Infants with BPD-PH have four times greater mortality risk than those with BPD alone, with estimates ranging from 21% to 50% (8–10). BPD-PH is also associated with increased risks of tracheostomy, feeding impairment, home oxygen use, hospital readmission, reduced neurodevelopmental outcome, and poor growth (11).

The approach to managing BPD-PH varies widely, including screening, diagnosis, treatment, use of cardiac catheterization, and pulmonary vasodilator therapy. Current guidelines recommend management of BPD-PH by a multidisciplinary PH team and initiation of sildenafil if PH remains after optimization of cardiac and respiratory disease management (12–15). Sildenafil has become a common treatment for patients with BPD-PH, and despite recommendations for cardiac catheterization prior to initiation of sildenafil (16), fewer diagnostic catheterizations are being performed (13, 17). However, the benefits of sildenafil remain unclear, as a meta-analysis including 101 patients concluded that sildenafil use in BPD-PH may be associated with improvement in pulmonary pressure and respiratory scores, but not mortality (18).

To improve care for BPD patients in the level IV neonatal intensive care unit (NICU) at Seattle Children's Hospital (SCH), a multidisciplinary inpatient BPD consult team was formed in 2017. Weekly consults were performed using a standardized approach to management of BPD-PH. Our team leveraged the synergistic expertise of all team members and prioritized optimization of respiratory support and treatment of comorbidities before initiation of PH medication. We now report the outcomes of the multidisciplinary systematic approach to BPD-PH at our center.

2. Methods

2.1. Patients and study design

The multidisciplinary BPD team consults on patients in our Level IV NICU who are >36 weeks PMA with severe BPD, or earlier at neonatology request for patients with evolving severe BPD. Referred patients are followed throughout their hospital course until discharge. All patients are out born and transferred due to need for pediatric subspecialty care, such as surgery or need for complex consultative care. We retrospectively reviewed records of all infants followed by the SCH BPD team during 2018–2020 for BPD-PH.

2.2. Management strategy for BPD-PH

The multidisciplinary inpatient BPD team was made up of pediatric specialists from neonatology, pulmonology, cardiology, critical care, respiratory therapy, feeding therapy, developmental therapy, and nutrition. Team members met weekly with the primary service teams to systematically review clinical events and trends, and to establish collaborative care plans. Screening and treatment for concomitant PH was discussed, including PH-specialist interpretation of the most recent echocardiogram. PH diagnosed in patients before 36 weeks PMA was considered "evolving" BPD-PH. **Figure 1** shows the algorithm for managing BPD-PH.

2.2.1. Optimization of respiratory support

Respiratory course was reviewed at each meeting, including symptoms, respiratory support, respiratory rates, oxy-hemoglobin saturations, chest imaging, laboratory values, and medications. Other data reviewed included length and weight trajectories, feeding tolerance, developmental progress, and rate of overall improvement. If BPD-PH was diagnosed, BPD respiratory support strategies (invasive mechanical ventilation, noninvasive positive pressure ventilation, continuous positive airway pressure, high flow nasal cannula) were optimized to minimize work of breathing, avoid hypercapnia, decrease hyperinflation, and support optimal growth and development consistent with strategies described by the BPD collaborative (4). As a team, we implemented the high tidal volume (10–14 ml/kg), low rate (16–20 breaths per minute), and long inspiratory time (0.5–0.7 s) ventilator strategy published by Abman et al., recognizing the need for unique ventilator management due to high airway resistance in severe established BPD. PEEP was clinically titrated to the individual patients' physiology based on the presence or absence of bronchoscopy-determined central airway malacia, severity of dynamic lower airway obstruction, and frequent bedside assessment of ventilator synchrony. In patients with frequent oxygen desaturations <94% despite bedside titration to goal, a minimum supplemental oxygen level (for example 0.25–0.3 FiO_2) was considered, but carefully balanced and frequently reassessed to avoid hyperoxia. Trials of systemic and inhaled steroids, diuretics, and inhaled bronchodilators were considered on a case-by-case basis. Chest computed tomography (CT) imaging of lung parenchyma and pulmonary veins, and airway endoscopy were obtained for cases with disproportionate hypoxia or hypercapnia, or persistent evidence of BPD-PH by echocardiogram despite optimization of respiratory support. Tracheostomy was considered for chronic respiratory failure requiring long term invasive ventilation. Optimization of respiratory support continued until the patient stabilized, growth normalized, neurodevelopmental progress was established, and BPD-PH improved.

2.2.2. Treatment of suspected aspiration

Patients with BPD-PH taking any oral feeds underwent clinical swallow evaluation and, if recommended, video fluoroscopic

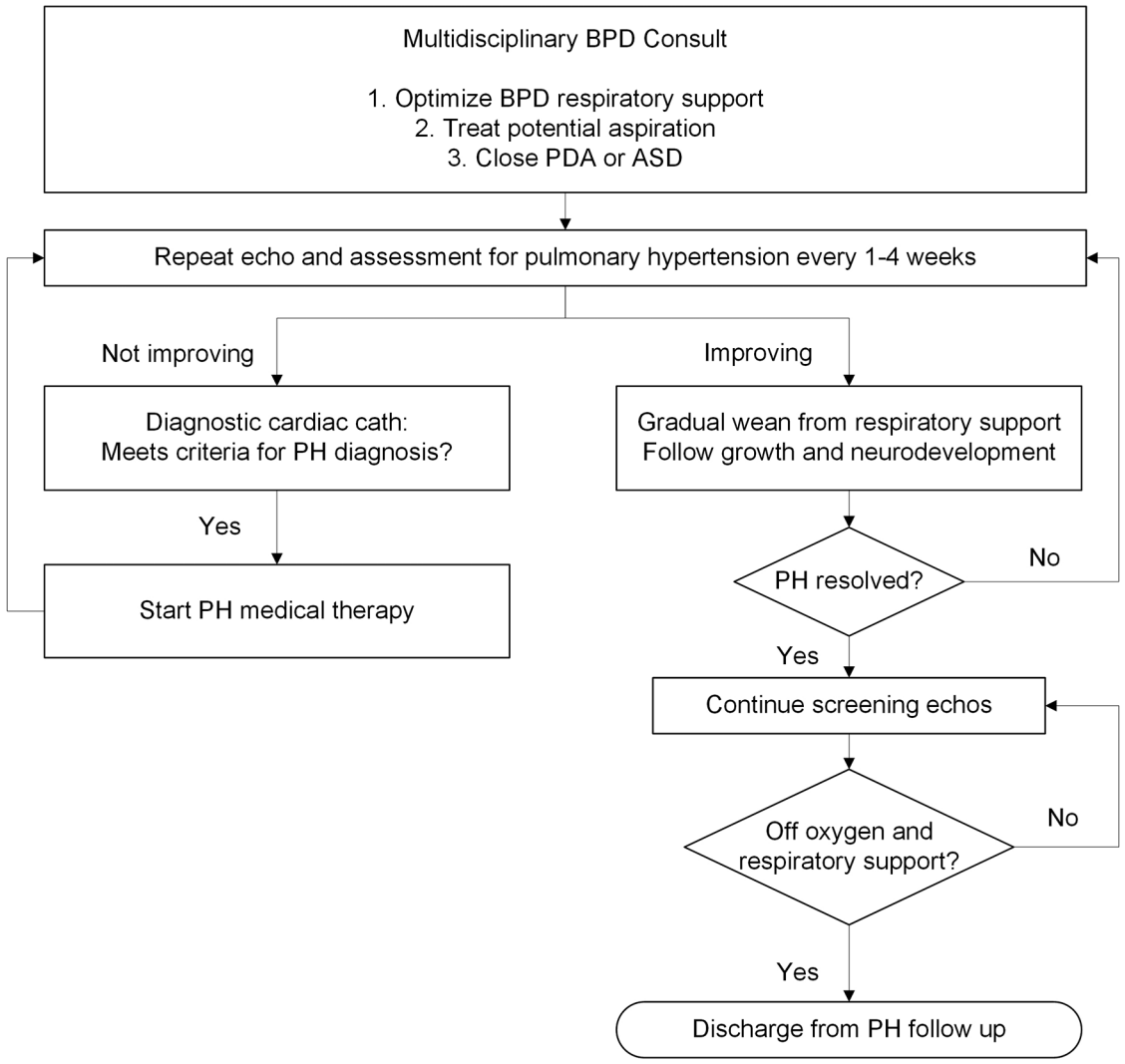

FIGURE 1
Algorithm of care for bronchopulmonary dysplasia-pulmonary hypertension (BPD-PH). PH, pulmonary hypertension; PDA, patent ductus arteriosus; ASD, atrial septal defect; Cath, catheterization; Echo, echocardiogram.

swallowing study. The feeding method was adjusted per feeding therapy and BPD team recommendations. Nasogastric feeding tubes were placed if needed to decrease aspiration risk and were changed from gastric to post-pyloric with concerns for significant reflux or aspiration, lack of respiratory status improvement, or worsening BPD-PH. Gastric feeds volumes and rate of delivery were adjusted to optimize feeding tolerance and minimize aspiration risk. Nissen fundoplication is not routinely performed at SCH, so all post-pyloric feeds were *via* nasoduodenal or gastrojejunal tubes.

2.2.3. Echocardiogram

PH was defined as tricuspid regurgitation jet > 2.5 m/s, interventricular septum flattened in systole, or bidirectional shunting in the presence of a patent ductus arteriosus (PDA) or ventricular septal defect. All echocardiogram images for this report were reviewed by a single cardiologist (DY). Screening echocardiograms were obtained according to our institutional protocols at or before 36 weeks PMA or at transfer to SCH for patients with BPD. Timing of echocardiograms before transfer to SCH was determined by the referring hospital, but images from most hospitals were available for our review. Available echocardiograms performed at day of life 7–14 were reviewed for early PH (19). Echocardiograms with PH, including those diagnosed before 36 weeks PMA, were repeated within 1–4 weeks depending on severity of PH and right ventricular failure. Repeat echocardiogram could also be triggered by rising B-type natriuretic peptide (BNP) levels, which were obtained concomitantly and between echocardiograms. Serial echocardiograms were also performed to follow-up PDA, atrial septal defect (ASD), and pulmonary vein stenosis (PVS), at a frequency determined by the PH specialist and cardiologist. After echocardiogram showed resolution of PH, screening echocardiograms continued every 1–6 months, depending on age and degree of respiratory and oxygen support, until patients were off all respiratory support.

2.2.4. PDA and ASD

Patients with a moderate or large PDA were recommended for cardiac catheterization for hemodynamic evaluation and potential closure by device at the time of BPD-PH diagnosis. Patients with moderate or large secundum ASD were recommended for device closure when BPD-PH did not resolve after optimizing respiratory support and treating aspiration. The devices used were the Amplatzer Piccolo Occluder, Medtronic Micro Vascular Plug and Siege Vascular Plug for PDA, and Amplatzer Septal Occluder device for ASD.

2.2.5. PVS

Patients with evidence of PVS on echocardiogram underwent chest CT angiogram and cardiac catheterization evaluation with possible intervention.

2.2.6. PH catheterization

Hemodynamic diagnostic catheterization before initiation of PH vasodilators, consistent with published recommendations (12), is standard practice at SCH. Patients who met the standard definition of PH, mean pulmonary artery pressure >20 mmHg, pulmonary capillary pressure <15 mmHg, and pulmonary vascular resistance >3 Woods units*m^2 (20), were considered for PH medical therapy.

2.2.7. PH medical therapy

Sildenafil was the first line pulmonary vasodilator after confirmation of PH by catheterization. Inhaled nitric oxide (iNO) was used before 36 weeks PMA in some mechanically ventilated infants with high FiO_2 at SCH and referring hospitals prior to transfer, but due to difficulty verifying this data, iNO use was not collected. Bosentan and prostacyclins were not used in this cohort.

2.3. Data collected

Supplementary Table S1 lists collected data.

2.4. Statistical methods

Analyses were conducted using R version 4.0.5. Descriptive statistics used for demographic and clinical characteristics included median/interquartile range (IQR) for continuous and counts/percentages for categorical variables. Length of time from BPD-PH diagnosis to resolution of BPD-PH was determined and presented as Kaplan-Meier plots (**Figure 2**). Potential outcomes of length of time to BPD-PH resolution were included in individual linear regression models with length of time to BPD-PH resolution as the predictor (**Supplementary Table S5**).

Log-rank tests (**Figure 2**) and individual linear regressions (**Supplementary Table S6**) were performed to test whether BPD-PH diagnosed before 36 weeks PMA (evolving BPD-PH) or small for gestational age (SGA) (21) status were associated with length of time to resolution of BPD-PH as predictors. A chi-squared test was used to test for association between echocardiographic evidence of PH on day of life 7–14 and >36 weeks PMA (**Figure 3** and **Supplementary Table S7**). Missing data were excluded from all analyses, and no corrections for multiple testing were performed.

3. Results

3.1. Study cohort

A total of 91 infants had initial consultation by the multidisciplinary BPD team between 2018 and 2020. Ten patients with critical congenital heart disease (CHD) (**Supplementary Table S2**), defined as requiring surgery or catheter-based intervention in the first year of life (22), were excluded due to critical CHD being a major risk factor for death in prematurity (23–25) and the challenges defining whether PH was attributable to premature lung disease or CHD itself. Eleven patients who never had PH on echocardiogram were excluded. Ten patients who resolved BPD-PH before transfer to SCH were excluded due to lack of data and because the BPD team did not participate in management of BPD-PH. The final study cohort included 60 infants with BPD-PH (**Supplementary Figure S1**).

3.2. Characteristics of study cohort

Table 1 and **Supplementary Table S3** list demographics and common comorbidities for the study cohort. All patients had follow-up through December 31, 2021, and inpatients were followed through September 2022. Two patients who died before discharge have missing data at discharge. The median gestational age was 24.9 weeks (IQR 24.1–26 weeks) and 20% of the cohort was SGA. Patients were transferred to SCH at a median of 5.4 weeks (IQR 1.7–13.2 weeks) after birth. Patients had initial consult by the BPD team at a median of 37.6 weeks (IQR 34.8–42.5 weeks) PMA. Twenty-one patients had initial consults before 36 weeks PMA, the earliest at 30.9 weeks. Almost half of the cohort (47%) met the definition of severe BPD type 2 (invasive ventilation at 36 weeks PMA), 25% underwent tracheostomy, and 42% went home on oxygen. At discharge, the vast majority (90%) were tube fed and 20% were post-pylorically fed.

3.3. Deaths

There were three deaths, all after resolution of BPD-PH. Two patients died of complications of post-hemorrhagic hydrocephalus and ventriculoperitoneal shunt, at 11 and 21 months of age. One patient died after an airway emergency at home with tracheostomy change at 25 months of age.

3.4. PH diagnosis and resolution

The median (IQR) absolute age of first echocardiogram with PH was 2.5 (1.4, 8.2) weeks, and the median (IQR) PMA of first

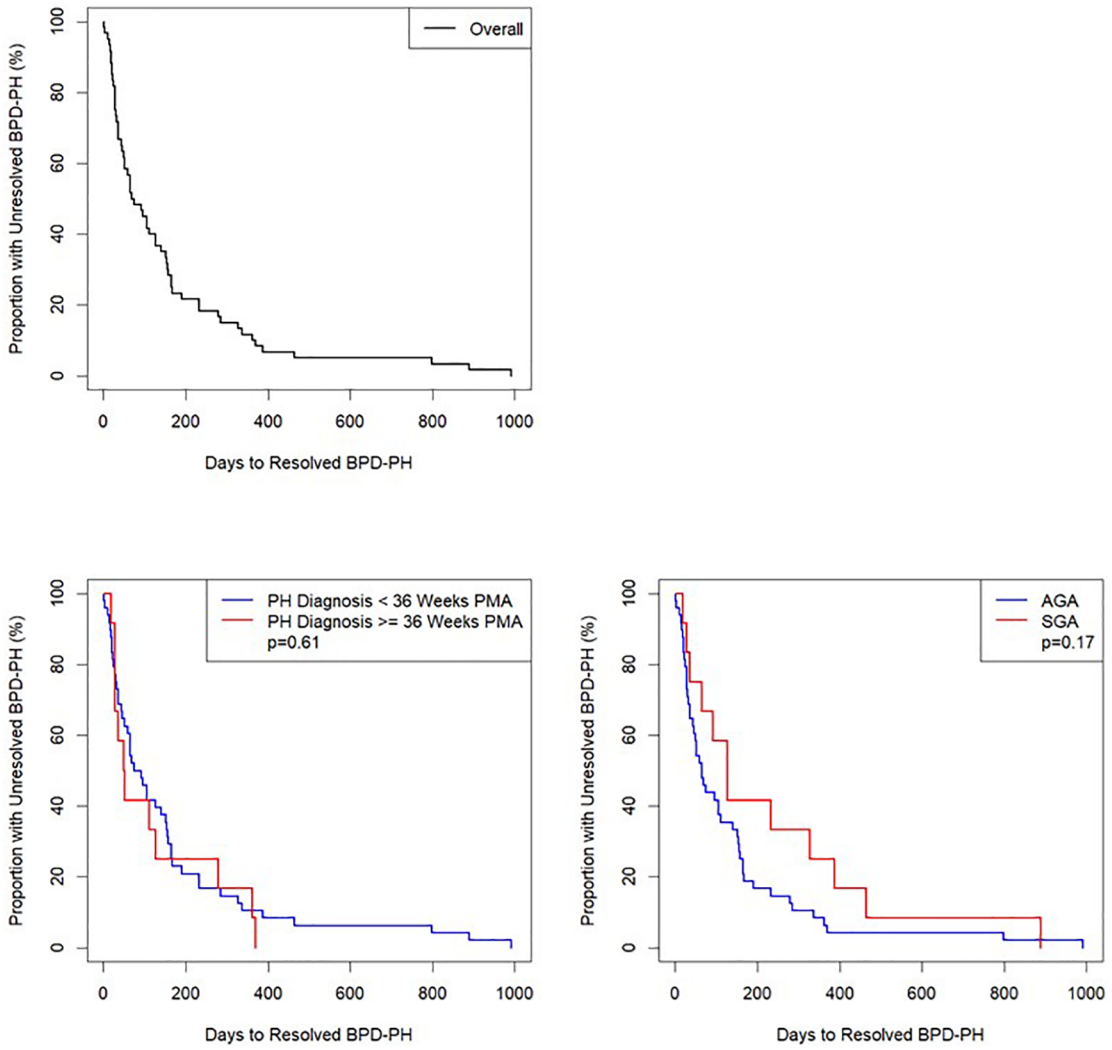

FIGURE 2
Kaplan–Meier curve of number of days from diagnosis to resolution of bronchopulmonary dysplasia-pulmonary hypertension (BPD-PH), $n = 60$. Top Left: entire cohort; Bottom Left: divided by BPD-PH diagnosed < or ≥ 36 weeks postmenstrual age (PMA); Bottom Right: divided by small for gestational age (SGA) or appropriate for gestational age (AGA). Log rank tests were calculated with significance defined as $p < 0.05$.

echocardiogram with PH was 28.1 (26.5, 33.4) weeks. BPD-PH was diagnosed before transfer to SCH in 29 (48%) patients. BPD-PH was diagnosed prior to 36 weeks PMA in 48 (80%) patients and after 36 weeks PMA in 12 (20%) patients.

BPD-PH resolved in all infants, including the three who died after resolution. The median (IQR) PMA of PH resolution was 43.5 (34.7, 55.8) weeks. BPD-PH resolved before 36 weeks PMA in 18 (30%) patients. In the group of 48 patients in whom BPD-PH was diagnosed before 36 weeks PMA, 30 continued to have BPD-PH after 36 weeks PMA. BPD-PH resolved between 36 and 52 weeks PMA in 24 (40%) patients, between 1 and 2 years of age in 15 (25%) patients, and greater than 2 years of age (specifically, 2.7, 3, and 3.3 years) in 3 (5%) patients. Thirteen (22%) had BPD-PH at hospital discharge.

The 26 patients who underwent cardiac catheterization for PDA closure resolved PH after a median (IQR) of 4 (0.3–16) weeks after PDA closure. Three patients who underwent ASD closure without PDA closure resolved PH after 1, 1, and 7 days.

Histograms showing PMA at BPD-PH diagnosis, BPD-PH resolution, and PDA or ASD closure are seen in **Supplementary Figure S2**.

3.5. PDA and ASD device closure

Twenty-four infants underwent successful cardiac catheterization for PDA closure alone, and one attempt was unsuccessful due to inferior vena cava clot and inability to establish access. Two patients underwent successful combined PDA and ASD closure and three underwent successful ASD closure alone. There were three catheterization complications during PDA closures: tricuspid valve damage in two patients and

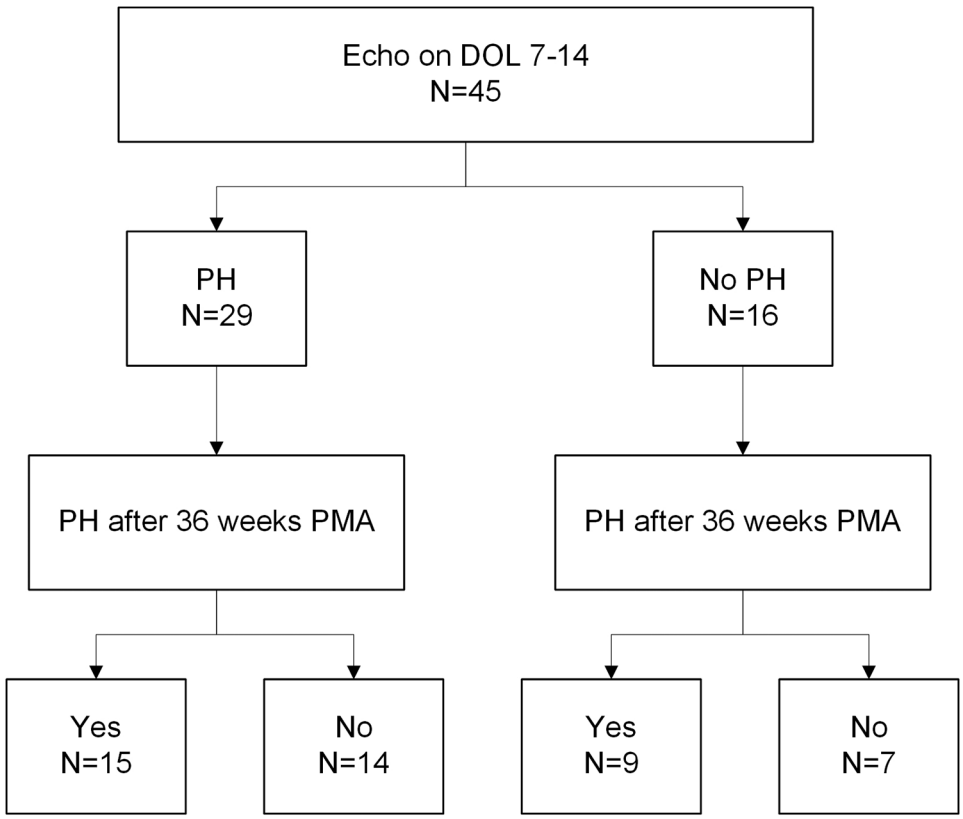

FIGURE 3
Flowchart of early echocardiogram PH diagnosis (DOL 7-14) and BPD-PH after 36 weeks PMA. Chi-squared test between groups has a *p*-value of 1. PH, pulmonary hypertension; BPD, bronchopulmonary dysplasia; DOL, day of life; PMA, postmenstrual age.

left pulmonary artery stenosis in one patient. There were no complications of ASD closure.

3.6. PH cardiac catheterization

Before eventual resolution of BPD-PH, three patients underwent diagnostic cardiac catheterization due to BPD-PH not improving by echocardiogram after respiratory optimization. Two met criteria for PH with mean pulmonary artery (PA) pressure >20 mmHg: 22 and 30 mmHg. In the third patient, catheterization revealed a significant shunt through a sinus venosus ASD as the cause of elevated mean PA pressure 21 mmHg, so the criteria for PH diagnoses was not met. Due to the location of the sinus venosus ASD, it had not been identified by echocardiogram and was not amenable to device closure. There were no diagnostic catheterization-related complications.

3.7. PH medication

Two patients diagnosed with BPD-PH by cardiac catheterization were started on sildenafil. The first patient had oxygen desaturation requiring an increase in the amount of supplemental oxygen to maintain oxygen saturation above 94% for 2–6 h following administration, resulting in discontinuation after the 4th dose. The second patient had urticaria and hypotension requiring treatment for anaphylaxis 21 days after initiation of sildenafil, and it was discontinued. BPD-PH resolved in both patients after discontinuation of sildenafil, the first at 58 weeks PMA and the second at 3 years of age.

Three additional patients were started on sildenafil without cardiac catheterization. One patient transferred to SCH at PMA 40.9 weeks and echocardiogram showed tricuspid regurgitation jet velocity 2.8 m/s; due to clinical instability iNO was transitioned to sildenafil at 1 mg/kg TID without cardiac catheterization data. PH resolved at 57 weeks PMA and the patient was allowed to outgrow sildenafil until the dose reached 0.5 mg/kg, after 41 weeks of treatment. Two other patients were transferred to SCH already on sildenafil. PH resolved after optimization of respiratory support, and sildenafil was stopped after the dose was outgrown to 0.5 mg/kg/dose after 15 and 36 weeks of therapy (**Supplementary Table S4**).

3.8. Outcomes and predictors of time to PH resolution

Time to PH resolution was not significantly associated with queried clinical outcomes (**Supplementary Table S5**). Neither

PH diagnosis <36 or ≥36 weeks PMA nor SGA status had significant individual associations as predictors of time to PH resolution (**Figure 2**, **Supplementary Figure S2**, and **Supplementary Table S6**)

3.9. PVS

Two patients underwent cardiac catheterization for PVS treatment. One patient developed PVS of the left upper, left lower, and right upper pulmonary veins at 15 months of age, in the setting of BPD-PH, and PH resolved by echocardiogram the day following PVS treatment. There have been multiple subsequent PVS interventions. The second patient developed PVS in the left upper pulmonary vein at 52 weeks PMA without associated PH after resolution of BPD-PH and did not have recurrence of PH or PVS after one intervention.

3.10. Early echocardiogram prediction of PH

To assess whether early echocardiograms at DOL 7 are associated with PH at 36 weeks in our cohort, we looked at the entire 91-patient cohort of severe BPD to include patients that never had PH. Of these patients, 45 had echocardiograms performed between day of life 7–14. We compared these to echocardiograms in the same patients at 36 weeks PMA for presence of BPD-PH (**Figure 3** and **Supplementary Table S7**). The chi-squared test *p*-value was 1, indicating no significant association between BPD-PH diagnosis in early and later echocardiograms.

TABLE 1 Demographic and clinical characteristics of patients with bronchopulmonary dysplasia-pulmonary hypertension (BPD-PH) (*n* = 60).

Variable	*N* (% of 60) or median (IQR)
Gestational age (weeks)	24.9 (24.1, 26)
Birthweight (g)	668 (590, 860)
SGA (20)[a]	12 (20%)
Male sex	39 (65%)
Race/Ethnicity (includes overlap)	
Any White	33 (55%)
Any Black	11 (18%)
Any Asian	8 (13%)
Any Hispanic	12 (20%)
Any Native American/Alaska Native	2 (3%)
Any other	2 (3%)
Declined to answer	2 (3%)
Age at transfer to center (weeks)	5.4 (1.7, 13.2)
PMA at transfer to center (weeks)	30.9 (26.6, 38.5)
PMA at diagnosis of BPD-PH (weeks)	28.1 (26.5, 33.4)
Died	3 (5%)
BPD Severity Type 2 (3)[b]	28 (47%)
ROP[c]	51 (85%)
IVH[c]	32 (53%)
NEC	21 (35%)
Invasive ventilation days	62 (34, 106)
Noninvasive positive pressure support days	80 (12, 128)
Missing data	9 (15%)
Tracheostomy	15 (25%)
Supplemental oxygen at discharge	25 (42%)
Missing data	2 (3%)
Feeding tube at discharge	54 (90%)
Missing data	2 (3%)
Post-pyloric feeds at discharge	12 (20%)
Missing data	2 (3%)

SGA, small for gestational age; PMA, postmenstrual age; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.
[a]See reference.
[b]Severe BPD type 2 = invasive ventilation. See reference.
[c]See Supplementary Table S3.

4. Discussion

4.1. Principal findings

4.1.1. BPD-PH diagnosis and resolution

Our cohort of patients with severe BPD all had resolution of BPD-PH with a strategy of multidisciplinary team care including optimization of respiratory support and interventional cardiac catheterization device closure of PDA and ASD, with limited use of sildenafil (8%) and low mortality (5%). To treat BPD-PH, we employed BPD-specific ventilator strategies, including low rate, higher tidal volume, longer inspiratory time, and PEEP titrated to treat multi-level airway disease (4). A quarter of the patients in our cohort required tracheostomy. Unlike respiratory strategies for younger premature infants, only mild hypercapnia was permitted with target pCO_2 less than 55 mmHg, and oxygen was added to achieve goal saturations above 94%. Respiratory support was considered optimized if infants demonstrated acceptable growth, minimal work of breathing, and could participate in developmental therapies. Outpatients with improving BPD-PH on respiratory support continued echocardiogram screening until BPD-PH eventually resolved, some taking over 2 years. Our team was also aggressive in treating potential aspiration as recommended by PH experts (26), with 90% of study patients discharged with a feeding tube and 20% on post-pyloric feeds.

BPD-PH was diagnosed relatively early, with half diagnosed before 2.5 weeks of life and 28.1 weeks PMA, and 48% diagnosed before transfer to SCH. Resolution occurred before 36 weeks PMA for 30%, between 36 and 52 weeks PMA for 40%, and after 52 weeks for 30%. In this large series of infants who received aggressive care for PDAs, BPD-PH resolution occurred a median of 4 weeks after device closure of moderate or large PDA. We note disproportionate representation of SGA in our cohort (20%), consistent with publications identifying SGA as a risk factor for development of PH in patients with BPD (27). However, despite being implicated as risk factors for severity of disease (19, 27), neither SGA nor PH diagnosis at PMA < 36 weeks were associated with length of time to PH resolution, suggesting that our multidisciplinary care may have negated some of the risks associated with these factors.

These results are similar to a cohort reported by Altit et al. in which the "natural history" of BPD-PH was resolution, although

their population was solely those with BPD-PH diagnosed after 36 weeks, with markers of more severe BPD, over a time period of nearly two decades (28). However, our cohort had lower mortality (5%) with the rare deaths unrelated to BPD-PH or heart failure. While we expect one result of our team-based approach to be lower mortality, the retrospective nature of this study and lack of an adequate historical control group makes it impossible to confirm causality. We hope with prospective data collection and improved guidelines for timing of referral for patients with severe BPD that we will be better able to address the impact of our multidisciplinary team in the future through single and multicenter studies.

4.1.2. High rates of intervention for PDA and ASD

Cardiology management played an important role in our management of BPD-PH, with almost half of the patients undergoing PDA or ASD device closure. Assessment and closure of both PDA and ASD were supported by recent findings that the presence of a PDA and an ASD is associated with increased risk of BPD-PH over time (29, 30). We used PDA and ASD size, not hemodynamic significance, as the indication for closure. This is because while a large PDA is not hemodynamically significant if there is high PVR, a large PDA will transmit systemic pressure to the pulmonary arteries. In addition, an ASD that causes even mild pulmonary over-circulation can lead to respiratory compromise in patients with lung dysplasia (30, 31). Historically, PDAs were surgically ligated, but newer devices make PDA and ASD closure in the cardiac catheterization lab an option with an acceptable level of risk in even very small infants. Likewise, while ASDs have not previously been considered important to the development of PH in neonates or infants and are generally recommended for closure in childhood before school age, the ability to safely close ASD in infants at SCH influenced our management recommendations and may have contributed to rapid resolution of BPD-PH. Contrary to conventional teaching to leave PDA or ASD as a "pop-off" in the setting of low velocity or bidirectional shunting, there has been no instance of right ventricular failure after closure in our cohort. This practice has been developed with the interventional cardiology team at our center, with whom we are fortunate to have a close collaboration.

4.1.3. Low sildenafil use

Our results show much lower use of sildenafil in the BPD-PH population (8%) than in other reports, including the multicenter Children's Hospital Neonatal Consortium, in which sildenafil use averaged 60% per center (11). We suspect our lower sildenafil use was due to several factors. First, the presence of BPD-PH on the echocardiogram signaled that respiratory support was sub-optimal and would guide changes in multidisciplinary team recommendations. Also, instead of initiating sildenafil when the echocardiogram continued to show BPD-PH after respiratory optimization, we elected to watch and reassess if the echocardiogram demonstrated improvement in BPD-PH. In addition, by having a cardiology-trained BPD team member comparing echocardiogram images, subtle improvements in BPD-PH not noted in the official echocardiogram report could be observed. Lastly, we are committed to diagnosing PH by cardiac catheterization, for reasons as discussed in **4.1.4.** below.

Furthermore, we speculate that even the three patients on long-term sildenafil may have resolved PH without treatment. We noted that the two patients who stopped sildenafil early due to adverse events and still eventually resolved BPD-PH were clinically similar to the third patient who was started on sildenafil by our group. In addition, BPD-PH resolved after involvement of our care in the two patients who were started on sildenafil by the referring hospital.

Whether higher use of sildenafil without diagnostic cardiac catheterization would have led to even earlier resolution of BPD-PH is unknown. However, increased sildenafil exposure would have increased risk of adverse events. The two adverse events that led to stopping sildenafil were well-documented and agreed upon by all team members. Hypoxemia in one patient after initiation of sildenafil may be due to lack of hypoxic vasoconstriction, leading to ventilation—perfusion mismatching, as others have speculated in BPD (32). Although many reports have demonstrated sildenafil safety in neonates (18, 33), we share concerns for unintended impacts of sildenafil on vascular development, such as those raised after sildenafil-exposed fetuses demonstrated increased risk of neonatal PH (34). We look forward to the results of a placebo-controlled clinical trial studying safety of sildenafil in BPD that is currently under way (35).

4.1.4. Cardiac catheterization diagnosis of PH

While our practice is to perform cardiac catheterization to diagnose PH, recently published work supports the empiric initiation of sildenafil without cardiac catheterization due to catheterization-associated risks, lack of clinical utility, and cost (17). Because we perform fewer cardiac catheterizations and initiate sildenafil less frequently, diagnostic cardiac catheterization before sildenafil initiation appears to have a beneficial role in our practice and patient population. This practice also allows for identification and treatment of other cardiac pathologies such as hemodynamically significant sinus venosus ASD as identified in one of our patients.

4.1.5. Echocardiogram screening of PH

Standards for timing and interpretation of screening echocardiogram for BPD-PH or elevated pulmonary pressures associated with evolving BPD remain unclear (36, 37). However, echocardiogram screening for PH before 36 weeks may influence early approaches to mitigate PH, such as ventilator strategies, PDA/ASD closure, and avoidance of aspiration. In our cohort, PH at DOL 7-14 echocardiogram was not associated with late PH at 36 weeks PMA, in contrast to findings from Mourani et al. (19). However, we acknowledge that our contemporary cohort is notably smaller with variable timing of echocardiograms and therefore may not provide accurate representation of early PH in the evolving BPD population across other centers.

4.2. Strengths

This is a contemporary cohort treated after publication of BPD-PH management guidelines (4, 12, 15, 38). Our population of patients with severe BPD was comparable to other published level IV NICU cohorts with respect to severity of BPD, gestational age, birth weight, and complications of prematurity such as IVH, NEC, and ROP, with a high level of acuity as a multistate regional referral center (39). Patient selection for inclusion in BPD rounds was objectively defined. Patients were treated by the BPD team in a systematic way, starting with screening echocardiograms, diagnosis, and treatment of BPD-PH. Echocardiogram images were reviewed by a consistent reader (DY), addressing the limitations of this modality and potential for subjectivity. Follow-up included echocardiography at least 1 year out in all infants, including evaluation beyond resolution.

4.3. Limitations

We acknowledge limitations of this retrospective review. Our analysis may provide insight but cannot confirm causality. Specifics of respiratory support optimization are not further delineated but were titrated to varying BPD phenotypes and associated physiologies (40). We relied heavily on the combined expertise of our specific subspecialties in fine-tuning respiratory support, including significant contributions of dedicated respiratory therapists. We were not involved in treatment before transfer to SCH and did not reliably have access to details of prior management or prior echocardiograms. Diagnosis of PH by echocardiogram remains somewhat subjective, and in cases without measurable tricuspid regurgitation, may be overestimated if using flattening of the interventricular septum. Hemodynamics were not assessed at cardiac catheterization for most patients who were catheterized specifically for device closure. We did not describe BNP trends due to an excess of values for assessment. Use of postnatal steroids, diuretics, and inhaled beta agonists was not evaluated. Due to this cohort starting in 2018 with follow-up through 2021, we are not able to evaluate if there are any patients who present as older children or adults with PH (41, 42). Small sample size may limit power to identify predictors and outcomes of time to PH resolution.

4.4. Clinical relevance

BPD-PH managed by a multi-disciplinary team, including optimization of respiratory support and early closure of PDA and ASD, may lead to improved mortality and resolution of BPD-PH, with low rates of pulmonary vasodilator use. Comparable time to resolution in patients anticipated to have persistent disease due to early diagnosis and/or SGA status supports this approach. Continuity of team members was key to recognizing subtle improvement, or lack thereof, and to tracking progress over time. Input from bedside nurses, respiratory therapists, nutritionists, physical therapists, occupational therapists, and feeding specialists was also essential to care. While optimizing respiratory status may lead to longer time on more invasive respiratory support, it likely allows for BPD recovery with both somatic and lung growth. In addition to following clinical progress, frequent screening echocardiograms evaluating the trajectory of BPD-PH should be used to guide whether respiratory support is optimized. Based on our lower usage of sildenafil, hemodynamic cardiac catheterization before initiation of sildenafil remained useful to confirm diagnosis of BPD-PH. While sildenafil remains first line medical therapy (33) for BPD-PH, we think it is prudent to await the results of ongoing and future research to best guide usage.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Seattle Children's Research Institute. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

DY, EJ, GR, RD, JM, LE performed the conceptualization, design, and methodology. DY, EJ, AB, MR, SB, LE performed data curation. DY, WT and LE performed formal analysis. DY drafted initial manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer SB declared a shared affiliation with the author AB to the handling editor at the time of review.

Publisher's note

Supplementary material

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EDITED BY
Catherine Avitabile,
Children's Hospital of Philadelphia,
United States

REVIEWED BY
Rachel Sullivan,
Vanderbilt University, United States
Angela Bates,
University of Alberta, Canada

*CORRESPONDENCE
Presley R. Crowell
✉ parulan1@texaschildrens.org

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Prevalence of malnutrition in pediatric pulmonary hypertension cohort and role for registered dietitian involvement

Presley R. Crowell[1]*, Mackenzie R. Frederick[1], Rozmeen A. Fombin[2], Nidhy P. Varghese[3] and Fadel E. Ruiz[3]

[1]Department of Clinical Nutrition, Texas Children's Hospital, Houston, TX, United States, [2]Department of Pulmonary Medicine, Texas Children's Hospital, Houston, TX, United States, [3]Department of Pediatric Pulmonology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, United States

Introduction: Pediatric pulmonary hypertension (PH) is a serious condition with increased risk for malnutrition due to increased caloric needs and reduced energy intake. This combination of disease and dynamic elements make it particularly challenging to meet expected growth patterns. Pediatric PH patients require close monitoring and individualized nutrition interventions to best meet nutrient needs. The prevalence of malnutrition and effective nutrition interventions in pediatric PH has not been studied.

Methods: Using our electronic medical record (EMR) patient care dashboard, malnutrition prevalence was assessed by reviewing the active problem list of all active PH patients at our center. A chart review compared patients with diagnosed malnutrition in the EMR to those with malnutrition identified by a registered dietitian (RD) using a standardized tool. Chart reviews also assessed outcomes of RD interventions.

Results: 195 patients were identified as active PH patients followed by our PH center during the study period (November 2021 to January 2023). Of these, 5% (10/195) had an ICD-10 code for malnutrition listed in their chart. However, upon further chart review of the remaining 185 patients, 22% (41/185) had malnutrition identified by a RD using Texas Children's Malnutrition Tool, totaling 51/195 (26%) malnourished patients. The PH RD saw 25/51 (49%) patients during PH clinic visits in the study period. At follow up visits (3–4 months after initial assessment), 56% (14/25) patients seen by the PH RD either improved or resolved their malnutrition status by *z*-score assessment.

Conclusion: Malnutrition is present in pediatric PH, although underappreciated and underdiagnosed. Managing malnutrition in pediatric PH requires close monitoring, multidisciplinary involvement, and individualized nutrition recommendations. This is best achieved by a dedicated PH RD who is familiar with the unique needs of this population and available to provide consistent nutritional assessments and interventions to reduce malnutrition in this population.

KEYWORDS

malnutrition, registered dietitian, pediatric nurition, nutrition assessment, pulmonary hypertension

Introduction

Pediatric malnutrition is defined as an imbalance between nutrient requirements and nutrient intake that results in deficits of energy, protein, or micronutrients that may negatively affect growth, development, and long-term health outcomes (1, 2). Even with the knowledge of increased consequences of pediatric malnutrition, pediatric populations continue to suffer from undernutrition. This condition is often underreported, and underappreciated. Prior studies have found malnutrition was only coded in 4% of hospitalized pediatric patients, despite reports of rates of 24%–50% of pediatric hospitalized patients (2).

Patients with chronic disease are at an increased risk for developing malnutrition due to increased energy expenditure. Malnutrition in the setting of chronic illnesses can be multifactorial, requiring complex individualized nutrition interventions. In addition, poor nutritional status can be an independent predictor of morbidity and mortality (3). A study by Luo and associates found that in adult pulmonary hypertension (PH) patients, poor nutritional status was associated with increased risk of adverse outcomes, including death. Worsening nutrition status was also linked to poorer lung function on pulmonary function tests (4).

Chronic lung disease in general increases energy expenditure and energy needs for growth in children; the same is true for those with cardiovascular disease. Therefore, pediatric PH has increased risks of malnutrition in an already vulnerable patient population. Limited research has been done to examine the energy requirements of adults with PH, and even less research is available on energy requirements for pediatric PH patients (5). One study conducted by Blasquez and associates examined nutrition status of children under the age of 2 with congenital heart disease (CHD). This study found moderate to severe malnutrition was significantly more common in children with PH. This study also found that those with PH had limited energy intake compared to those with CHD alone and those with PH had inadequate nutrition support (6). The combination of increased energy needs coupled with decreased intake puts pediatric PH patients at elevated risk for poor growth, chronic malnutrition, and negative health outcomes (7). For these reasons, pediatric PH patients are a unique group of children who require close monitoring and individualized nutrition interventions to meet growth expectations. Unfortunately, there is currently no validated screening process or standardized nutrition recommendations to address these specific nutrition concerns related to pediatric PH.

We therefore aimed to understand the prevalence of physician-diagnosed malnutrition in our PH cohort, compare this to rates of malnutrition identified by standardized assessment and examine nutritional outcomes of PH-dedicated Registered Dietitian (RD) assessment and intervention. We expected that increased RD involvement by a designated PH RD would improve weight gain, body mass index (BMI)/weight-for-length *z*-scores and overall nutrition status.

Methods

This was a single center, retrospective cohort study of pediatric patients with diagnosed PH from November 2021 to January 2023. The study population included all active patients with PH managed at our PH center during the study period. Identified charts were assessed for ICD-10 codes for malnutrition (ICD 10- codes E43, E44, E46), which were listed in the active problem list of the EMR. Texas Children's dietitians applied the Texas Children's Pediatric Malnutrition Tool (**Table 1**) to the remaining active patient charts without ICD-10 code of malnutrition for missed malnutrition diagnoses. Analysis compared rates of malnutrition diagnosed and listed in the EMR to malnutrition identified by a RD. RD consults and nutrition interventions were assessed from November 2021 to January 2023 for impacts of RD involvement in the outpatient setting on malnutrition status.

Results

195 patients were active during the study period (**Table 1**). Five percent (10/195) of patients at our PH center had an ICD-10 code for malnutrition in the EMR. Additional manual chart review of remaining 185 active PH patients identified an additional 41 (41/185, 22%) patients who met malnutrition criteria using the Texas Children's Hospital Pediatric Malnutrition Tool (**Figure 1**).

Of the 51 total patients identified with malnutrition, 27 patients (53%) were classified as mild malnutrition, 13 patients (25%) as moderate malnutrition, and 11 patients (22%) with severe malnutrition based on stratification of body mass index (BMI)/weight-for-length *z*-scores. Of note, severity of malnutrition approximated severity of PH. **Table 1** shows malnutrition tended to occur more commonly in patients with moderate to severe PH. Severe malnutrition was more commonly seen in patients with New York Heart Association (NYHA) functional class ≥2, and mild malnutrition appeared more common in those with NYHA functional class 1. Of note the malnourished patient population was found to have higher prevalence of other comorbidities compared to the total PH patient population. Statistical analysis of the association between severity of PH and malnutrition status could not be performed due to sample size limitations (see **Table 1**).

Twenty-five of the 51 malnourished patients were seen by the PH RD for nutrition assessments. The remaining 26 patients were not seen due to RD coverage, inadequate time in clinic, virtual visit types or physician failure to consult RD. The designated PH RD screened clinics and reassessed malnourished patients typically every 3–4 months until patients met growth expectations and/or malnutrition status improved. Nutrition assessments included initial RD assessment of caloric intake and growth patterns. Fourteen of the 25 (56%) patients who had RD involvement either improved or resolved their malnutrition status based on improvement in BMI *z*-score at follow up PH clinic visits during the study period (see **Figure 2**).

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TABLE 1 Patient characteristics.

	Active PH patient cohort	Malnourished PH patients	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Age					
0–2 year	33	11	6	2	3
3–6 years	62	17	9	3	5
7–10 years	41	11	6	3	2
11–15 years	41	9	5	3	1
16–18 + years	18	3	1	2	0
Gestational age					
22–28 weeks	24	6	5	1	0
29–32 weeks	16	5	0	2	3
33–37 weeks	59	17	12	4	1
38 + weeks	91	21	10	4	7
Unknown	5	2	0	2	0
Provider documented PH severity					
Mild	67	12	7	4	1
Moderate	62	16	12	1	3
Severe	40	14	4	5	5
Resolved	16	6	4	1	1
Unknown/undocumented Severity	10	3	0	2	1
NYHA functional class					
1	71	14	10	4	0
2	69	19	9	6	4
3	14	4	2	1	1
4	4	3	1	1	1
Undocumented	37	11	5	1	5
Gastrostomy tube in place					
Yes	76	26	11	7	7
No	119	25	16	6	4
Comorbidities as per medical problem list					
Bronchopulmonary dysplasia	26	7	5	1	1
Congenital heart disease[a]	168	26	12	7	7
Chronic lung disease	15	15	5	4	6
Obstructive sleep apnea	17	3	1	0	2
Trisomy 21	32	3	3	0	0
Restrictive lung disease	4	0	-	-	-
Congenital diaphragmatic hernia	19	12	7	2	3
Other genetic diseases, known syndromes or associations[b]	28	12	6	5	1

[a]Congenital heart disease: hypoplastic left heart syndrome, atrial septal defect, ventricular septal defect, atrioventricular septal defect, patent ductus arteriosus, patent foramen ovale, pulmonary vein stenosis, Scimitar syndrome, single ventricle physiology.
[b]Genetic diseases or known syndromes/associations: Noonan syndrome, DiGeorge syndrome, Wolff Parkinson White syndrome, Ehlers-Danlos syndrome, Cantú syndrome, autoimmune disease not otherwise specified, cerebral palsy, Trisomy 18, Scimitar chromosomal duplication not otherwise specified, Adams Oliver syndrome, tetrasomy 9p, hereditary hemorrhagic telangiectasia gene mutations, Jeune syndrome.

Discussion

PH has many risk factors for abnormal nutrition status. Dyspnea is a common symptom of PH. In addition to increasing energy needs, oral intake with dyspnea may be limited due to poor coordination of breathing and swallowing, with associated risk of dysphagia and aspiration. This increased effort can prevent adequate calorie consumption and may require the use of enteral nutrition support to safely meet elevated energy needs. Additionally, prolonged hospital stays decrease the ability to practice age-appropriate feeding skills and increases the incidence of oral aversions, which can limit age-appropriate foods consumed and further decrease caloric intake (9). Use of nutritional supplements or enteral nutrition support may therefore also be needed to meet calorie and protein needs in patients with oral aversions. Finally, medications used to manage PH symptoms may cause nausea, diarrhea, decreased appetite, and further decrease oral intake. The combination of increased energy needs coupled with decreased intake puts pediatric PH patients at elevated risk for poor growth, chronic malnutrition, and negative health outcomes due to decreased vitality (7). For these reasons, pediatric PH patients are a unique group of children who require close monitoring and individualized nutrition interventions to meet growth expectations.

Primary Malnutrition Indicators – Single Data Point

Primary Indicators	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight-for-height z score	-1 to -1.9 z score	-2 to -2.9 z score	≥ -3 z score
BMI-for-age z score	-1 to -1.9 z score	-2 to -2.9 z score	≥ -3 z score
Length/height z score	No data	No data*	-3 z score
MUAC (6-60 months)	≥ -1 to -1.9 z score	≥ -2 to -2.9 z score	≥ -3 z score

Primary Malnutrition Indicators – Two or More Data Points

Primary Indicators	Mild Malnutrition	Moderate Malnutrition	Severe Malnutrition
Weight gain velocity (<2 years of age)	<75% of the norm for expected weight gain	<50% of the norm for expected weight gain	<25% of the norm for expected weight gain
Weight loss (2-20 years of age)	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight for length/height z score	Decline of 1 z score	Decline of 2 z score	Decline of 3 z score
Inadequate nutrient intake	51-75% estimated energy/protein need	26-50% estimated energy/protein need	≤25% estimated energy/protein need

FIGURE 1
Texas children's hospital pediatric malnutrition tool (8).

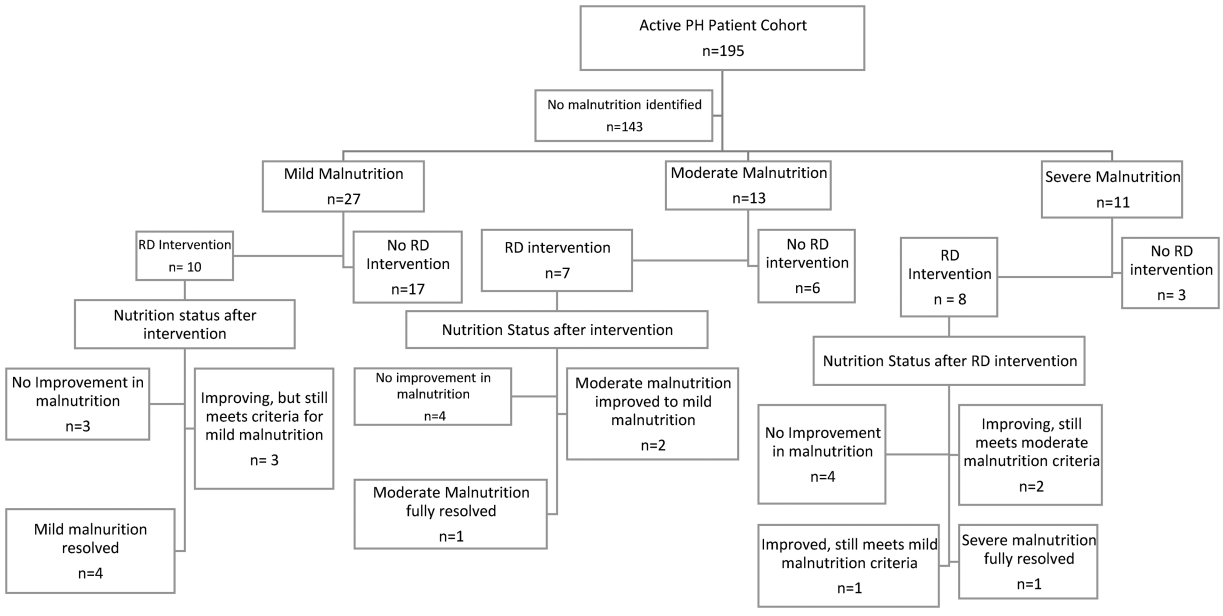

FIGURE 2
Flowchart of results.

In our cohort, only 5% of patients had a diagnosis of malnutrition listed in the EMR. However, manual chart reviews found malnutrition was prevalent at much higher rates of 26% (51/195) using a dedicated nutritional screening tool. The Texas Children's Malnutrition Tool is a standardized tool that is used throughout the institution to screen and assess for malnutrition

(8). Per hospital policy, it is required for RDs to document using Texas Children's Pediatric Malnutrition tool upon identification of malnutrition. RDs receive extensive training on how to use the Texas Children's Pediatric Malnutrition Tool in multiple hospital settings to accurately identify malnutrition. RD findings of malnutrition are documented within provider encounters.

Our study found that malnutrition was commonly not coded as a medical problem, resulting in decreased team awareness of malnutrition, missed opportunities for RD consultation and fewer occasions for interventions to address malnutrition. At our institution, physicians are responsible for adding and identifying appropriate malnutrition ICD-10 codes. However, with an embedded RD in clinic and commitment for yearly nutritional screening, collaboration with a PH RD will improve accurate identification of malnutrition and promote essential communication among the medical team. This is essential for improved EMR capture of the malnutrition burden of nutritional concerns in this population and allow for appropriate interventions to reduce severity. Prior to the study period, RD assessments were on a consultation basis only. These were most often for poor weight gain, weight loss, decreased intake, or adjustments of enteral nutrition support. Dietitian interventions for these consults included introducing nutrition supplements, modifying enteral nutrition feeding regimens, and educating families on high calorie foods. In addition to assessments, RDs assisted providers in ordering nutrition supplements and specialty enteral formulas to best meet patient needs. Advocating and facilitating access for patients to receive necessary supplies to meet their increased energy needs was a recognized crucial component of RD involvement to improve nutrition outcomes. Unfortunately, during this period, patients were seen on a consult-only basis and there was no structured RD follow up nor tracking of consultation. On average, staff RD were consulted on 4–6 patients per month.

In November 2021, our PH center acquired a designated PH RD to have embedded support within the clinic, to increase access to consultation and intervention. The PH RD communicated with families in between PH clinic appointments on a bi-weekly to monthly basis to ensure growth patterns were following age-appropriate recommendations. Oral nutrition supplements and enteral nutrition were assessed and adjusted as indicated to meet constantly fluctuating energy needs due to changes in activity, intake, or acute illnesses. Nutrition reassessments were conducted as determined by the PH RD if growth remained below recommended for age, suboptimal intake continued, or malnutrition persisted. On average, the PH RD consults on 25–30 new and follow up patients per month. RD re-assessments in PH clinic are conducted 3–4 months after the initial RD assessment.

Active interventions, close monitoring and frequent follow up by a designated PH dietitian improved or resolved malnutrition status in 56% of patients followed by the PH RD from November 2021 to January 2023. Our findings supported our expectation that increased RD involvement by a designated PH RD would be associated with improved weight gain, BMI/weight-for-length z scores and overall nutrition status.

Limitations of this study include single center study with a limited sample size. Inherent to retrospective chart review analyses, there may have been missed malnutrition diagnoses by providers and missed malnutrition documentation in the absence of RD consultation. We did not have year-over-year data to offer direct comparisons prior to November 2021, although this information is now available for future tracking. Although nutritional outcomes were improved, the study period was too short to identify other nutrition-related improvements on objective markers of PH disease severity such as hemodynamics. NYHA FC was not significantly affected by nutritional intervention since most children are FC I–II, consistent with registry data (10).

Conclusion

Nutritional assessment is a crucial component of comprehensive pediatric PH care. The vulnerable nature of pediatric PH requires close assessment and monitoring of energy expenditure and calorie supplementation by a trained dietitian who is familiar with nutritional requirements of children with cardiopulmonary disease. Our study found that a designated PH RD increased awareness of malnutrition and improved the nutrition status of many patients seen during a designated period at our PH center. The RD was able to identify patients at risk of developing malnutrition using a standardized screening tool and recommend appropriate nutrition interventions, which resulted in improved nutritional outcomes. Further studies to provide guidelines and dietary recommendations for this population are needed.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the (patients/participants OR patients/participants legal guardian/next of kin) was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

PC and MF performed the retrospective review and data collection. The conclusions and writing of the article were carried out by PC and MF, with the review of RF, NV, and FR. All

authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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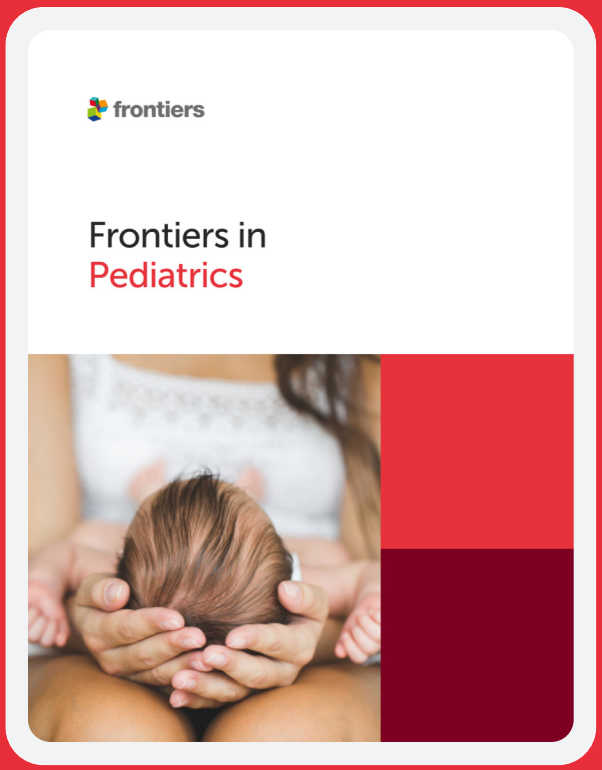

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