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Characterisation of paediatric pulmonary hypertensive vascular disease from the PPHNet Registry

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Abstract

Background—There are limited data about the range of diseases, natural history, age-appropriate end-points and optimal care for children with pulmonary hypertension (PH), including the need for developing high-quality patient registries of children with diverse forms of PH to enhance care and research. Our objective was to characterise the distribution and clinical features of diseases associated with paediatric PH, including natural history, evaluation, therapeutic interventions and outcomes, as defined by the World Symposium on Pulmonary Hypertension (WSPH) classification.

Methods—1475 patients were enrolled into a multisite registry across the Pediatric Pulmonary Hypertension Network (PPHNet), comprised of eight interdisciplinary PH programmes.

Results—WSPH Groups 1 (pulmonary arterial hypertension (PAH)) and 3 (lung or hypoxia-related PH) were the most common primary classifications (45% and 49% of subjects, respectively). The most common Group 3 conditions were bronchopulmonary dysplasia and congenital diaphragmatic hernia. Group 1 disease was predominantly associated with congenital heart disease (60% of Group 1 cases) and idiopathic PAH (23% of Group 1 cases). In comparison with Group 1, Group 3 subjects had better disease resolution (hazard ratio 3.1; $p<0.001$), tended to be younger at diagnosis (median (interquartile range) age 0.3 (0.0–0.6) *versus* 1.6 (0.1–6.9) years; $p<0.001$) and were more often male (57% *versus* 45%; $p<0.001$). Down syndrome, the most common genetic syndrome in the PPHNet Registry, constituted 11% of the entire PH cohort.

Conclusions—We find a striking proportion of paediatric PH patients with Group 3 disorders, reflecting the growing recognition of PH in diverse developmental lung diseases. Greater precision of clinical phenotyping based on disease-specific characterisation may further enhance care and research of paediatric PH.

Shareable abstract (@ERSpublications)

To characterise the clinical features of diseases associated with paediatric pulmonary hypertension, including natural history, evaluation and therapeutic interventions, longitudinal data from 1500 children from major PH programmes were analysed https://bit.ly/3ff3zjV

Introduction

Pulmonary hypertension (PH) and related pulmonary vascular diseases (PVDs) are associated with severe morbidities and high mortality in children, but little is known about the natural history, outcomes, age-appropriate end-points and optimal care for children with diverse forms of PH [1–4]. Although there have been major advances in the field, PH continues to cause significant morbidity and mortality in diverse pulmonary, cardiac, haematological and other systemic disorders of childhood [2–4]. The long-term outcomes of children with severe PH remain poor despite the availability of new drug therapies, as most clinical trials have been performed in adult patients and these drugs are used off-label for paediatric PH.

Despite some similarities, many aspects of PH in children are distinct from adult PH [3–5]. Paediatric PH is often intrinsically linked to issues of lung growth and development, as well as many genetic, prenatal and early postnatal influences [2], and there are marked

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differences in the epidemiology of paediatric and adult PH [6–12]. The Pediatric Task Force at the recent 6th World Symposium on Pulmonary Hypertension (WSPH; Nice, France, 2018) reported that striking differences exist in function, structure, genetics and responsiveness to therapies between adults and children with PH [4]. Randomised clinical trials and case studies that address the safety and efficacy of PH therapies in children are rare, as most pharmaceutical studies have focused on the adult population and primarily in patients with a fairly limited range of associated conditions.

Paediatric PH is associated with diverse disorders that have distinct pathogenetic mechanisms, clinical courses and outcomes from adult disease that remain poorly characterised [2–5]. There remains a major need to understand the diversity of paediatric PH, the prevalence of each disease within PH groups, disease-specific features (such as age of onset, diagnostic and therapeutic approaches, interventions, and outcomes), and the utility of the current classification systems to better characterise comorbidities and to identify phenotypes or subgroups within each of the disease categories. Given this disease heterogeneity, high-quality patient registries with large numbers of patients and related databases of children with diverse forms of PH are necessary to better define the epidemiology of paediatric PH, disease subgroups, and the current status of PH evaluation and therapies.

Over the past decades, the original World Health Organization (WHO) classification system of PH has progressively evolved to characterise different forms of PH, as most recently updated at the WSPH in 2018 [13]. Although primarily designed for use in adult PH, the current version of the WSPH classification has been amended in response to the Pediatric Task Force of the WSPH to design a comprehensive system that is readily useful for children [4]. The importance of developing a useful classification for children includes the need for clarifying disease phenotypes, encouraging novel understanding of disease causation and pathobiology, enhancing diagnostic evaluations, improving correlations of phenotype and therapeutic responsiveness, and optimising clinical trial design. Most importantly, such systems may further promote successful outcomes by facilitating strategies more directly supportive of “precision medicine” [14–19].

Based on the WSPH classification, past registry reports of children with PH have provided important insights into the spectrum of paediatric PH [6–11]. These registries are partly limited, however, by the relatively narrow scope of patient selection by PH group, the inherently biased nature of referrals, relatively small patient numbers, cardiac catheterisation as a required inclusion criteria and the nature of clinical practice of PH centres participating in the registries that may not reflect broader, multidisciplinary programmes. Due to these limitations, past registries may not directly capture the “real-world” nature of PH in children, in which multiple factors may contribute to underlying disease severity and outcomes.

We sought to define the epidemiology of patients based on the WSPH classification using a multicentre prospective registry of paediatric PH patients. Specifically, in order to measure the scope and current landscape of paediatric PH, we developed a multisite registry with the following goals: 1) determine the proportion of newborns, infants and children with PH of

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diverse aetiologies as defined by the WSPH classification system; 2) fully characterise and define clinical features, current diagnostic and therapeutic approaches, and outcomes of the diverse conditions associated with paediatric PH; and 3) characterise the outcomes, age of disease onset and disease progression or resolution, within each of the WSPH diagnostic categories.

Methods

Study design

We developed an extensive registry enrolling subjects with diverse forms of paediatric PH from eight well-established academic PH centres throughout North America that constitute the Pediatric Pulmonary Hypertension Network (PPHNet) [2]. The multicentre registry captured electronic reports of comprehensive clinical data from October 2014 to April 2020, which was partly supported by a National Heart, Lung, and Blood Institute-funded U01 program. The study protocol was approved by the institutional review boards of all participating centres, and all study participants, parents and/or guardians signed informed consent. Assent was obtained in patients according to institutional guidelines. Inclusion criteria included newborns, infants, older children and adolescents who were diagnosed prior to 18 years of age as having PH, which was defined according to established guidelines for paediatric PH from the American Heart Association (AHA)/American Thoracic Society (ATS) [5]. We followed the diagnostic criteria based on the AHA/ATS Consensus Guidelines Statement, which was developed from member sites of PPHNet along with others (table 1 in [5]). These criteria are similar to the WSPH criteria, which state that "the definition of PH in children has been the same as in adults, *i.e.* mean pulmonary arterial pressure (mPAP) ⩾25 mmHg. In the normal fetal circulation, PAP is similar to systemic pressure and rapidly falls after birth, achieving levels that are similar to the adult by 2–3 months of age. Due to variability in pulmonary haemodynamics during post-natal transition, paediatric PH has been defined as mPAP ⩾25 mmHg after 3 months of age" [4]. We further consider estimated PAP over half-systemic in infants younger than 3 months of age as meeting the criteria [4, 5]. We did not use the newer WSPH standard of mPAP >20 mmHg, as this change in recommendations came after the initiation of the current study. Echocardiographic or haemodynamic evidence of PH was required for all enrolled subjects. Although cardiac catheterisation was often performed as part of the diagnostic evaluation, it was not required for enrolment and differences between sites may reflect different practice patterns or scope of practice [5].

Although patient evaluation and care was directed by each site, clinical management generally followed the consensus recommendations and guidelines for paediatric PH as previously published [4, 5, 20]. This further included the approach of PPHNet sites to the management of PH in former preterm infants with chronic lung disease, which has been the subject of intense discussions and became the standard of care for our centres prior to this work [20].

Case report forms for data collection were developed in working groups among the PPHNet investigators, and included extensive clinical, demographic, haemodynamic data, laboratory information, drug therapies and outcomes, along with other parameters (as described in the

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following data collection and analysis section). Accuracy and completeness of data entry into the electronic database was monitored throughout the data collection period through biweekly data quality committee meetings, development and review of data quality queries, and coordination with site principal investigators.

Clinical data were entered into the secure web-based platform (Medidata; www.medidata.com) and included group assignment as based on designation according to the classification from the 5th WSPH held in Nice in 2013, which was established at the time of the initiation of the PPHNet Registry [2]. Each patient was assessed and classified by site investigators by primary aetiology into one of the five of the established groups: Group 1, pulmonary arterial hypertension (PAH); Group 2, PH associated with left heart disease; Group 3, PH associated with lung and hypoxia-related causes; Group 4, chronic thromboembolic PH (CTEPH); and Group 5, systemic and multifactorial disorders (figure 1).

Data collection and analysis

Descriptive statistics include counts (percentages) for categorical variables and mean with standard deviation or median (interquartile range (IQR)) for continuous variables. Patient and disease characteristics and management factors for WSPH Groups 1 *versus* 3 were compared using a Chi-squared test for categorical measures and the t-test or Wilcoxon rank sum test for continuous measures. Kaplan–Meier methodology was used to estimate the distribution of time from the diagnosis of PH to the composite outcome of death or lung transplant, with group comparisons by the log-rank test. The distribution of time to death or transplant using the entire cohort was estimated using risk set delayed-entry methodology. The Fine–Gray subdistribution proportional hazards model was used to estimate time from the diagnosis of PH to the earliest occurrence of a qualifying event in a competing risks framework (death *versus* lung transplant *versus* PH resolution). The competing risks analysis was restricted to the incident case cohort, defined as cases with a PH diagnosis on or after the inception of the PPHNet Registry (October 2014). For PH patients in WSPH Groups 1 and 3 (with the exception of Eisenmenger syndrome patients), PH resolution was defined as the cessation of PH-targeted medications (calcium channel blockers, endothelin receptor agonists, phosphodiesterase type 5 inhibitors, prostacyclin, inhaled nitric oxide and selexipag). For patients with PH-targeted medication stops and restarts, the latest date on record for cessation of PH-targeted medications was used as the event time, not the initial date of cessation. In addition, all tables in this article that depict Group 1 include Groups 1′ and 1″, unless otherwise noted. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.5.1 (www.r-project.org).

Results

Overall cohort

The analytic cohort was comprised of 1475 patients (table 1). The majority of patients were diagnosed between 2005 and 2017 (supplementary figure S1). There were 782 patients diagnosed prior to October 2014 (designated as the prevalent cohort) and 693 diagnosed in October 2014 or later (incident cohort). The cohort was 51% male, with a median (IQR)

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age at diagnosis of PH of 0.5 (0.1–3.6) years. The racial distribution was 61% White, 13% Black, 9% Asian and 17% Other/Unknown; 16% of patients were of Hispanic ethnicity. The range of enrolment of patients from the eight registry sites was 94–286 patients, and the distribution of subjects from each centre that comprise total enrolment within the primary categories of Group 1 (PAH) and Group 3 (lung or hypoxia-related PH) varied from 8% to 22% and 4% to 25%, respectively, which likely represent differences in scope of practice among the PH programmes. We recruited both incident and prevalent cases into the PPHNet Registry. Approximately half (53% (782 patients)) were diagnosed prior to the start of the Registry in October 2014 and the remaining 47% (693 patients) were diagnosed after the start of the Registry, with the vast majority enrolled within months of PH diagnosis. We examined the distribution of WSPH classification for the two groups and found no major systematic differences. With respect to persistent PH of the newborn (PPHN) (a total of 50 patients), 22% of those enrolled were prevalent (11 patients) and 78% were incident (39 patients). There were 58 Group 2 patients and 44% *versus* 56% of these cases were prevalent *versus* incident compared with the overall ratio of 53%/47%.

Figure 1 and tables 1–3 present the distribution of subjects enrolled in the PPHNet Registry according to the WSPH classification system. Patients categorised in Group 3 disease (lung or hypoxia-related PH) comprised 49% of subjects. Group 1 (PAH) was the second largest group, which included 45% of enrolled patients. Group 1 diseases were predominantly associated with congenital heart disease (CHD) (60%) and idiopathic PAH (23%). The other groups, including Group 2 (left heart disease; n=54) and Group 5 (systemic diseases; n=30), were far more infrequent and only eight subjects with Group 4 (CTEPH) were identified during the study period. As a result, further characterisation and analysis primarily focused on Group 1 and 3 disorders.

Characterisation by WSPH group

As shown in table 1, Group 3 patients were more often male compared with Group 1 patients (57% *versus* 45%; p<0.001). Median (IQR) age at diagnosis was younger (p<0.001) for Group 3 (0.3 (0–0.6) years) *versus* Group 1 patients (1.6 (0.3–6.9) years). White subjects constituted 61% of the overall cohort, which was higher than the proportion of Black (13%), Asian (9%) or Other/Unknown (17%). There was no association between WSPH group and Hispanic ethnicity; however, race was associated with WSPH group (p<0.001), even after adjusting for study site (p=0.008). Black race was more common in Group 3 than Group 1 (15% *versus* 10%; site-adjusted p=0.009) and Asian race was more common in Group 1 than Group 3 (13% *versus* 6%; site-adjusted p=0.001). There was no difference in the distribution of White subjects between Groups 1 and 3. Descriptive statistics for subgroups within Groups 1 and 3 (the largest primary classifications) are provided in tables 2 and 3, respectively. CHD constituted nearly 60% of Group 1 disease, with idiopathic and heritable PAH diagnosed in 23% and 6% of Group 1 patients, respectively (table 2). The majority of Group 1 patients were characterised by: Eisenmenger syndrome in 4.1%, systemic-to-pulmonary shunts in 7.7% and post-operative PAH in 19.1% (combined partial and total repair). Subjects with PPHN (Group 1″) represented only 7.6% of the study population.

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Within the Group 3 category, infants with developmental lung disease, especially bronchopulmonary dysplasia (BPD) and congenital diaphragmatic hernia (CDH), were the largest subgroups, representing 22% and 17% of all PPHNet Registry subjects, respectively (44% and 36% within the Group 3 cohort, respectively) (table 3). Although subjects with interstitial lung disease accounted for 4% of patients in Group 3, no patients with cystic fibrosis were enrolled, which may reflect the later onset of PH outside of the paediatric age range in this important subgroup. Secondary WSPH classifications are displayed in supplementary table S3.

Genetic causes of identified cases of heritable PAH (table 4) and genetic syndromes associated with PH (table 5 and supplementary table S1) are provided. Down syndrome was the most common diagnosis among the genetic syndromes (11% of all PPHNet Registry subjects) and *BMPR2* gene mutation was the most frequent cause of the known heritable cases (17 out of 40 patients; or 43% of identified cases with heritable disease in the PPHNet Registry).

Associations with WSPH group

Differences in diagnostic evaluations were noted between the WSPH groups (supplementary table S2). Group 1 subjects had higher rates of ECG studies (76% *versus* 51%; p<0.001) and cardiac catheterisations at PH diagnosis than Group 3 patients (70% *versus* 30%; p<0.001), whereas Group 1 subjects more often had pulmonary function testing (7% *versus* 2%; p<0.001) and chest computed tomography scans (26% *versus* 13%; p<0.001). At cardiac catheterisation, median (IQR) pulmonary vascular resistance index was higher in Group 1 (9.0 (5.0–16.1) WU) than in Group 3 subjects (5.8 (4.3–8.3) WU; p<0.01) (supplementary table S2). Assessment of 6-min walk distance (6MWD) was less common in Group 3 (1%) than Group 1 (12%) patients, which likely reflects age differences between groups.

Functional class (FC) at diagnosis as assessed by the standard WHO definitions and by age-related recommendations (the Pediatric FC [21]) are shown in figure 2 and supplementary table S4. At diagnosis, the distributions of FC for the 503 patients evaluated by WHO criteria differed for Groups 1 and 3 (p=0.011), primarily due to the lower percentage of patients in FC I (17% *versus* 28%, respectively). For both groups, over one-third were in FC groups III and IV (38% and 40%, respectively). According to assessment with the Panama Pediatric FC criteria [22], which was used for the evaluation of 791 subjects, 58% of the overall cohort presented as meeting FC IIIa, IIIb and IV criteria, which was more common (p<0.001) in Group 3 (68%) than Group 1 (48%) (supplementary table S4).

Medication use in the overall cohort and according to WSPH group is shown in table 6. Medications are reported from the time of enrolment into the PPHNet Registry, at a median of 1.3 years following diagnosis of PH. Group 3 patients were less likely to be treated with PH medications than Group 1 (50% *versus* 78%; p<0.001). The proportions of patients on monotherapy were similar (37% for Group 3 and 34% for Group 1), but more subjects in Group 1 were treated with combination therapy (table 3). Group 1 patients who received PH medications were more likely to be treated with endothelin receptor antagonists (34% *versus* 10%; p<0.001) and prostacyclin or prostacyclin derivatives (27% *versus* 6%; p<0.001). At enrolment, 62% of Group 1 and 47% of Group 3 patients were prescribed

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PH-associated medications (p<0.001). Among those taking other medications, aspirin use was more common in Group 1 (16% *versus* 3%; p<0.001), as well as coumadin (10% *versus* 1%; p<0.001).

Clinical outcomes

The median (IQR) follow-up duration of the transplant-free survivors was 4.1 (2.0–7.4) years. We first examined lung transplant-free survival for differences according to the inception date of the PPHNet Registry (October 2014). The composite incidence of death or lung transplant was lower (p<0.001) for the prevalent cohort (*i.e.* those diagnosed prior to October 2014), suggesting the expected survivor bias in enrolment, compared with the incident cohort (diagnosed later) (figure 3a). However, the distribution of WSPH groups was similar for the two cohorts. In the incident cohort, which had a median follow-up of 2 years, overall transplant-free survival was 92% (95% CI 90–94%) at 1 year and 84% (95% CI 80–87%) at 5 years. In the incident cohort, the difference in the distribution of death/transplant by WSPH group did not achieve statistical significance (p=0.09) (figure 3b). At 3 years post-diagnosis, transplant-free survival was 85% for Group 1 and 88% for Group 3. Group 2 (PH due to left heart disease, n=54) had 68% (95% CI 41–85%) transplant-free survival at 3 years. Based on the entire cohort with extended follow-up, we found a significant difference (p=0.010) in the distributions of death/transplant by WSPH group (figure 3c).

A competing risks analysis based on the Groups 1 and 3 incident cohort was performed. Outcomes, which included death, lung transplant and resolved PH (defined as cessation of PH medications; see Methods), are depicted in figure 4. For Group 1, 5-year event rates were 12% mortality, 2% lung transplant, 42% PH resolution and 44% alive transplant-free with PH. As shown, the patterns for Groups 1 and 3 disease differ with respect to disease resolution, with Group 3 subjects having a higher rate of PH disease resolution, as defined by being alive without requiring PH-targeted medications (resolution hazard ratio 3.1, 95% CI 2.6−3.7; p<0.001) than Group 1 patients. By 5 years post-diagnosis, event rates for Group 3 were 12% mortality, 1% lung transplant, 72% PH resolution and 15% alive transplant-free with PH. Figure 3a displays transplant-free survival for the entire PPHNet Registry cohort. While an underestimate of total events, there is a pattern of greater late mortality in Group 1 patients compared with Group 3 patients.

Examination of the entire cohort revealed that Group 1 patients who had PH disease resolution compared with those without resolution were diagnosed at an earlier age with PH (median 0.3 *versus* 3.6 years), more likely to have PPHN (Group 1″; 23% *versus* 2%) and were more often in Pediatric FC I or II (59% *versus* 48%). They did not differ with respect to the presence of CHD or with respect to gestational age. The Group 3 patients who had PH disease resolution compared with those without resolution were diagnosed with PH at a somewhat earlier age (median 0.2 *versus* 0.4 years), were more likely to have CDH (41% *versus* 25%) and were more likely to be in WHO FC I or II (69% *versus* 48%).

Discussion

Despite advances in our understanding of its pathobiology and the growing availability of PH-specific drug therapies, PH and related PVDs in children continue to cause significant

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morbidity and mortality. Paediatric PH is highly heterogeneous and has been understudied. Relatively little is known about the basic disease mechanisms, natural history, long-term outcomes, age-appropriate clinical end-points and optimal therapeutic strategies for children with PH and clinically important subsets [2–5]. To address these critical problems and to assess disease phenotypes, we developed an extensive patient registry of children with PH at large interdisciplinary programmes and characterised PH-related diseases as categorised by the 5th WSPH classification system from 2013. Although slightly modified during the 6th WSPH in 2018 [4], the system outlined in the previous symposium was used for this study due to the timing of the initiation of the PPHNet Registry. In contrast with past registry studies [6–11], we report that WSPH Group 3 disease (lung or hypoxia-associated PH) constitutes nearly half of the cases of paediatric PH, reflecting a greater recognition of preterm infants at risk for BPD, the impact of CDH and Down syndrome, and genetic causes of developmental lung diseases. This large dataset confirms substantial differences in the types and outcomes of PH between paediatric and adult patients, justifying discussions for the need to develop a new paediatric-specific classification system for PH patients.

We found important differences in demographic factors and clinical outcomes based on PH subtype, including better transplant-free survival and disease resolution, as defined by subjects who are alive off PH medications, in the Group 3 cohort in comparison with Group 1 disease. Subjects with Group 3 disease tended to be younger at diagnosis, were more often male and more frequently Black race than Group 1 children. Rates of cardiac catheterisation were lower in Group 3 than Group 1 children (30% *versus* 70%) and Group 3 subjects were more often treated with monotherapy *versus* combined PH-targeted therapies in comparison with Group 1 patients. Overall, these findings highlight the striking contribution of lung-related disease to the spectrum of paediatric PH and differences of treatment approach, and given the high prevalence of this PH type, underscore the important need for focused research and multicentre randomised trials of this understudied group.

High-quality patient registries of children with diverse forms of PH are important to better define the epidemiology and clinical features of paediatric PH. A helpful classification system would serve to enhance approaches to patient care and research that will improve the early identification or anticipation of PH in at-risk subjects; provide the correct primary diagnosis; guide the effective evaluation and therapies; enable rapid recognition of critical features, common comorbidities and disease modifiers; and develop disease-specific strategies. Improving the recognition of disease phenotypes provides a basis for establishing common approaches for understanding and treating subgroups of patients with PH to meet critical challenges of providing personalised care, and to provide a useful, pragmatic, consistent and easy to understand system that can be readily applied by clinicians from multiple sites.

Based on concerns that the WSPH classification system, largely an adult-focused system, may not sufficiently identify the phenotypic heterogeneity of childhood PH or meet the needs of paediatric providers, the Pediatric Task Force of the Pulmonary Vascular Research Institute (PVRI) proposed a novel classification that may prove useful as a paediatric-specific system [22]. The goals of the PVRI Panama Classification System are to highlight the phenotypic heterogeneity of PH and related PVDs throughout childhood and the impact

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on diagnosis, treatment and research. However, whether this system has greater clinical utility than the recently updated version of the WSPH classification system as recently modified by the Pediatric Task Force of the WSPH is uncertain [4].

In the Spanish paediatric PH registry, 61% of patients had PAH (Group 1), 14% had PH with left heart disease (Group 2), 18% had PH associated with respiratory disease (Group 3), 1% had CTEPH (Group 4) and 4.5% had multifactorial factors (Group 5), including metabolic diseases [7]. Of significance is that 31% of the patients had PH associated with multiple aetiologies, suggesting the need for more accurate phenotyping beyond traditional classification schemes alone. This study showed that independent risk factors for mortality included aetiology group, age at diagnosis younger than 2 years, advanced FC and high right atrial pressure as assessed by cardiac catheterisation. Among several unique observations from the Spanish registry is the important association of CHD in patients with lung disease or left heart disease with worse outcomes; notably, Group 2 PAH was not included in the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry [6]. As observed in other registries, patients with Eisenmenger syndrome or those with left-to-right shunts had better survival than patients with PAH and coincidental CHD or post-operative PAH. The PPHNet Registry has also confirmed previous findings that patients with Shone's complex or isolated pulmonary vein stenosis have a very poor prognosis [6–9].

The development of high-quality patient registries represents only the beginning of the extensive work that must be done to more precisely phenotype and characterise the natural history, disease course, response to therapies and late outcomes of paediatric PH. Rigorous registries provide an essential foundation for supporting deeper explorations of patient phenotypes and better identification of patient populations for clinical trials, as well as establishing useful study end-points and meaningful surrogates to enhance understanding and development of novel therapeutic strategies. These issues reflect the need to include collaborations with multidisciplinary teams (e.g. pulmonologists, neonatologists, intensivists, haematologists and others) to cast a far larger net that will more accurately reflect the epidemiology and nature of paediatric PH.

Previous publications from the few existing registries have begun to identify differences in the aetiology of PAH between adults and children [6–11]. Past reports from paediatric registries have primarily emphasised that WSPH Group 1 disorders, including idiopathic PAH, heritable PAH and PAH associated with CHD, constitute the majority of cases. For example, of the 362 patients included in the pharmaceutical-sponsored TOPP registry, 88% had PAH, including 57% with idiopathic PAH or familial PAH and 36% with PH associated with CHD [6]. Only 42 of the enrolled patients (12%) had PH associated with respiratory diseases, with BPD being the most frequent disorder. This is likely due to the requirement for cardiac catheterisation, as well as bias in registry enrolment due to scope of practice.

A potential limitation of these data is the use of the 5th WSPH classification system from 2013, rather than the most recent revision that followed the 6th WSPH in 2018, which was held after the initiation of this study. Although there may be some changes in disease classification [4], these specific changes are unlikely to significantly alter the findings of this report and allow for more direct comparisons with previously published registry data,

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as Group 1 and Group 3 diagnoses remained consistent between the two versions [4]. As this study required identification and consent for enrolment, not all patients enrolled at study sites represent sequential cases, which may have contributed to enrolment bias. Finally, these data further reflect the bias of case referrals to PH programmes for care at each site, e.g. many cases of milder forms of PPHN are managed without consultation.

Overall, we provide a characterisation of the scope of paediatric PH through an established patient registry as provided from a network of multidisciplinary academic centres that collectively provide the largest clinical experience with paediatric PH to date. This large dataset confirms substantial differences in the types and outcomes of PH between paediatric and adult patients, justifying discussions for the need to develop a new paediatric-specific classification system for PH patients.

As with previous registries, limitations include biased or selective enrolment that reflects differences in clinical practice, which raises questions regarding our ability to cast a sufficiently “wide net” as enrolled subjects depended upon multiple factors, including practice pattern, role of consultant services with PH and others. In addition, both prevalent and incident cases were enrolled, which will be useful for future association analyses, but we have restricted our event rate estimates in this article to the incident cohort. As discussed, cardiac catheterisation was performed in most but not all subjects, which better reflects current practice in many centres, especially in the setting of premature infants with lung disease (BPD) and developmental lung disorders, such as CDH, alveolar capillary dysplasia and others. Although academic programmes included within PPHNet provide interdisciplinary groups of investigators at each site, practice variations exist. There is a persistent need to more precisely define disease subgroups through computable phenotyping and/or use of biological markers (“-omics”) to provide endotypes within groups or to provide unique and distinct clusters between/among groups. We speculate that combining data from established patient registries with novel strategies that include data extraction from electronic health records and patient-reported outcomes will likely further enhance our ability to perform deeper phenotyping and personalised therapies in the near future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest:

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Institutes of Health, during the conduct of the study. J.P. Kinsella has nothing to disclose. The University of Colorado contracts with Actelion, Bayer, Gilead and United Therapeutics for D. Ivy to be a consultant and preform clinical research trials. R.K. Hopper has nothing to disclose. J.U. Raj has nothing to disclose. J. Fineman has nothing to disclose. R.L. Keller reports grants from the National Heart, Lung, and Blood Institute, during the conduct of the study. A. Bates has nothing to disclose. U.S. Krishnan has nothing to disclose. C.M. Avitabile has nothing to disclose. A. Davidson has nothing to disclose. M.D. Natter reports grants from the National Heart, Lung, and Blood Institute, during the conduct of the study. K.D. Mandl reports no specific conflicts, however in the interest of full disclosure, reports personal fees from Merck, and philanthropy from Eli Lily to his lab, during the conduct of the study.

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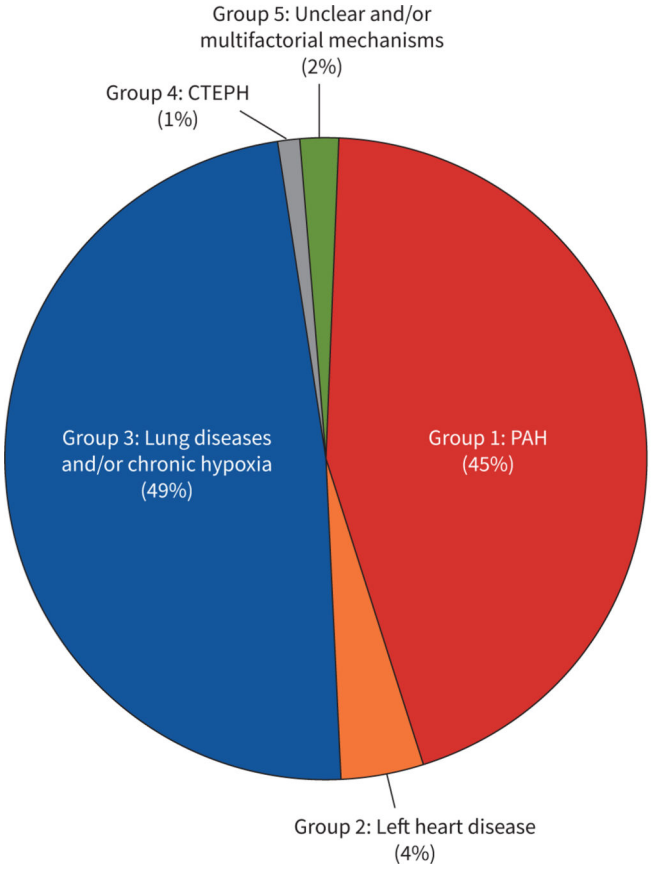

Group 1	PAH	602 (40.8%)
Group 1'	PVOD, PCH	11 (0.8%)
Group 1"	Persistent PH of the newborn	50 (3.4%)
Group 2	PH due to left heart disease	54 (3.7%)
Group 3	PH due to lung disease and/or chronic hypoxia	720 (48.8%)
Group 4	PH due to blood clots in the lungs	8 (0.5%)
Group 5	PH due to blood and other disorders	30 (2.0%)

FIGURE 1.

Distribution of children with pulmonary hypertension (PH) according to the World Symposium on Pulmonary Hypertension (WSPH) classification system. The proportions of subjects with paediatric PH are depicted according to the 2013 WSPH classification (n=1475 subjects). Group 3 disorders (lung or hypoxia-related PH) constitute the largest proportion of subjects in the PPHNet Registry followed closely by Group 1 (pulmonary arterial hypertension (PAH)). CTEPH: chronic thromboembolic PH; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis.

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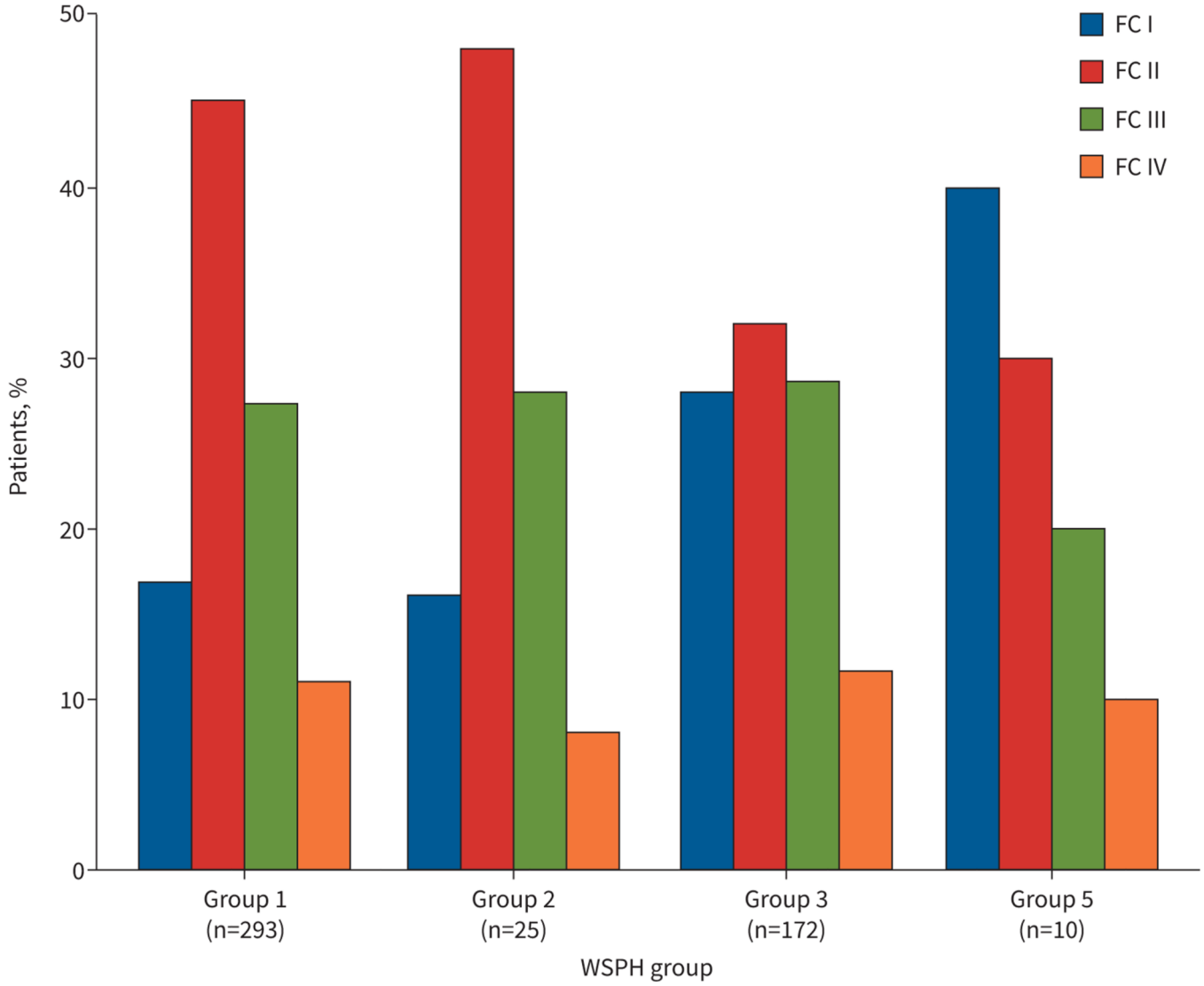

FIGURE 2.

World Health Organization (WHO) Functional Class (FC) at the time of pulmonary hypertension diagnosis (n=503). The distributions of WHO FC for World Symposium on Pulmonary Hypertension (WSPH) Group 1 and Group 3 differ (p=0.011). Group 4 is omitted due to few patients (n=3).

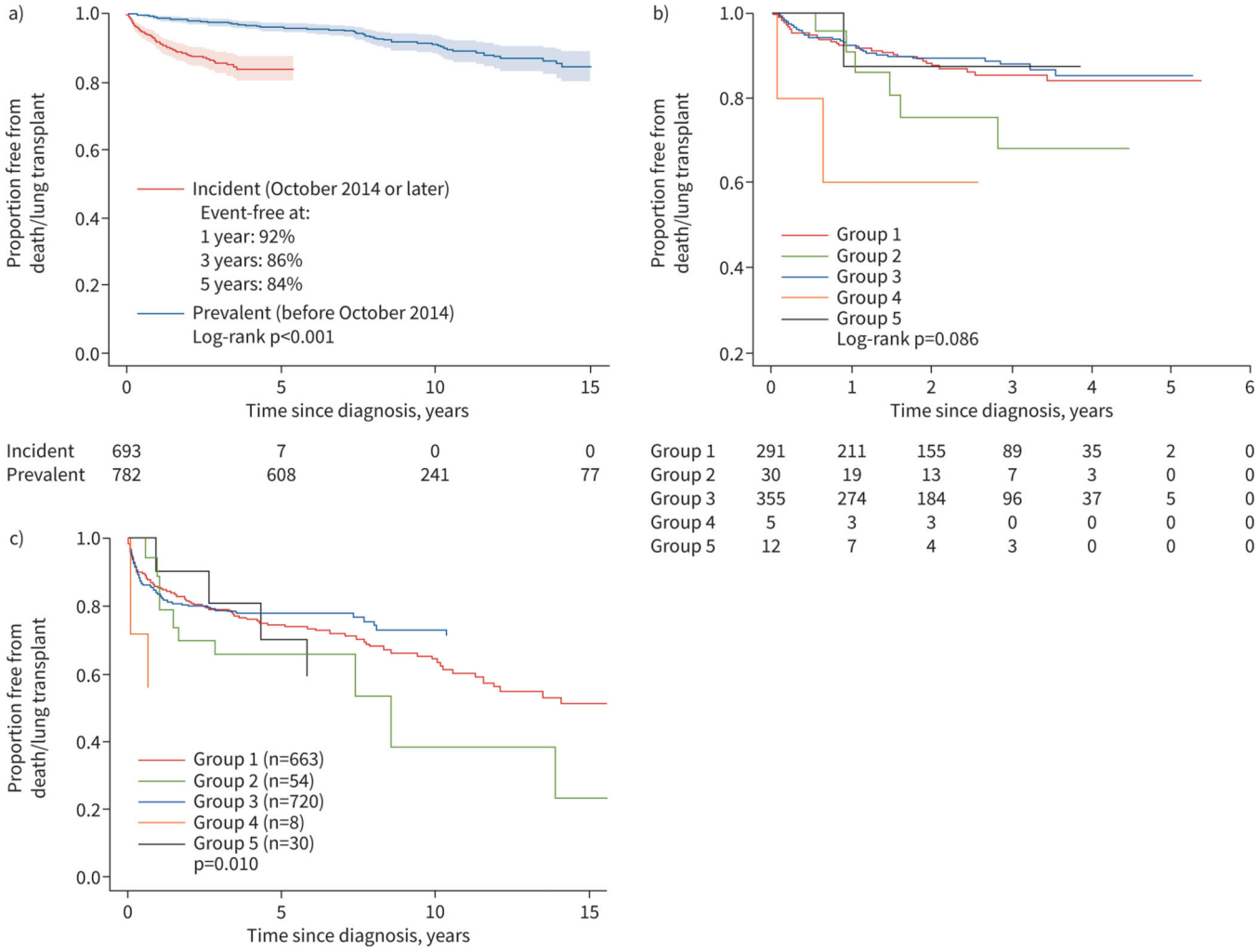

FIGURE 3.

Freedom from death/lung transplant for a) prevalent *versus* incident cases (defined as pulmonary hypertension diagnosis before *versus* after the inception date of the PPHNet Registry), b) by World Symposium on Pulmonary Hypertension (WSPH) group based on the incident cohort and c) by WSPH group for the full cohort. Follow-up is truncated at 15 years. Four deaths in the diagnosis prior to 2014 cohort occurred after 15 years and are not shown (n=3 Group 1 patients and n=1 Group 2 patient). Shaded regions denote pointwise 95% confidence bands.

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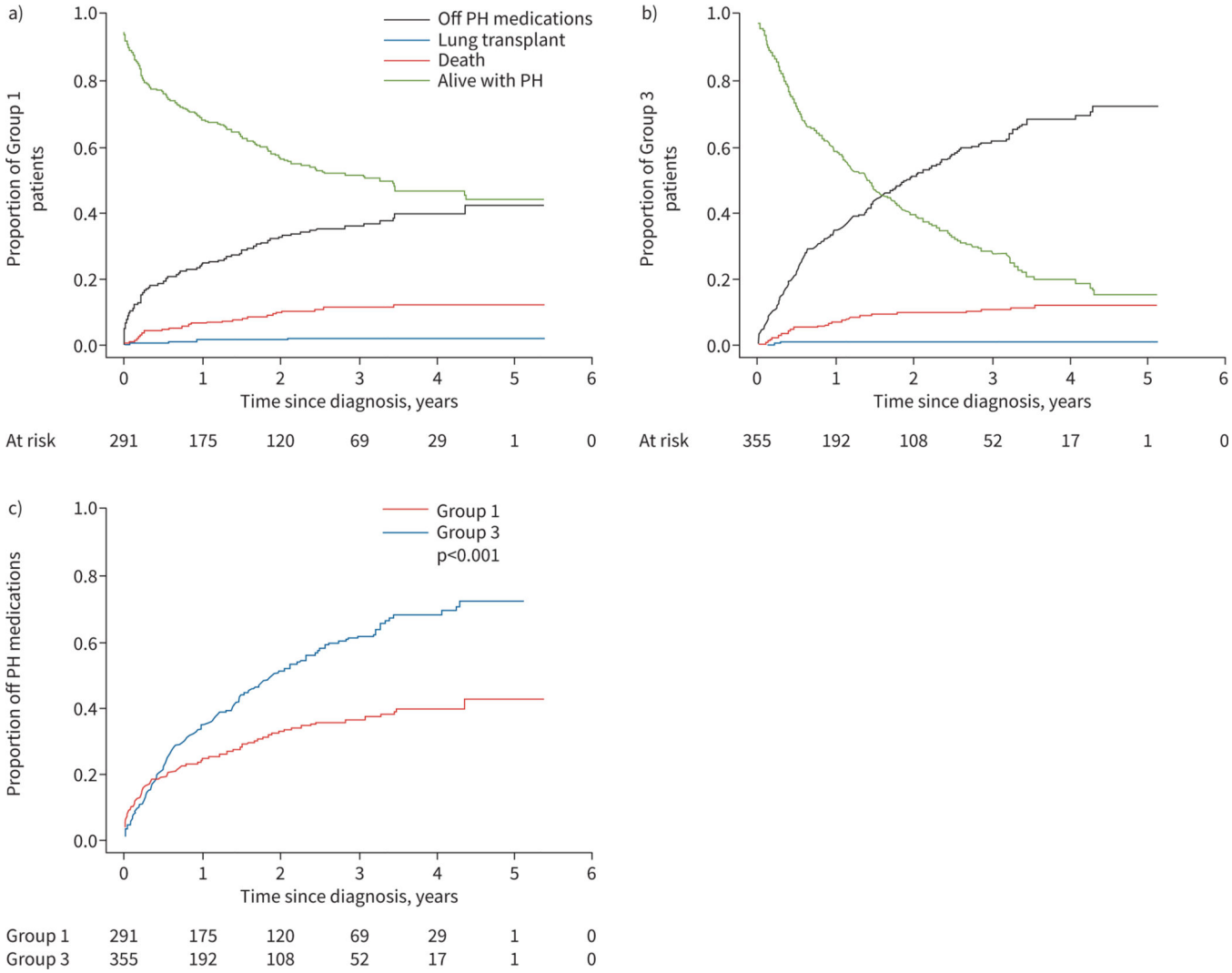

FIGURE 4.

Display of competing risks estimates including death, lung transplant, alive with pulmonary hypertension (PH) and alive off PH medications for the PPHNet Registry World Symposium on Pulmonary Hypertension (WSPH) a) Group 1 and b) Group 3 incident cohort. c) In comparison with Group 1 disease, longitudinal follow-up of patients within Group 3 demonstrates a pattern of greater rates of cessation of PH medications with lower mortality with time.

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TABLE 1

Demographic findings of the PPHNet Registry cohort by primary World Symposium on Pulmonary Hypertension (WSPH) group

	Overall (n=1475)	WSPH group					p-value
		Group 1 (n=663)	Group 2 (n=54)	Group 3 (n=720)	Group 4 (n=8)	Group 5 (n=30)	
Site							<0.001
Colorado	222 (15)	92 (14)	2 (4)	123 (17)	0 (0)	5 (17)	
Alberta	94 (6)	58 (9)	6 (11)	28 (4)	1 (13)	1 (3)	
Stanford	101 (7)	61 (9)	6 (11)	34 (5)	0 (0)	0 (0)	
Boston	286 (19)	90 (14)	10 (19)	178 (25)	2 (25)	6 (20)	
UCSF	111 (8)	58 (9)	2 (4)	47 (7)	2 (25)	2 (7)	
CHOP	260 (18)	109 (16)	7 (13)	139 (19)	1 (13)	4 (13)	
Vanderbilt	139 (9)	50 (8)	5 (9)	75 (10)	2 (2)	7 (23)	
Columbia	262 (18)	145 (22)	16 (30)	96 (13)	0 (0)	5 (17)	
Male	758 (51)	296 (45)	31 (57)	413 (57)	3 (38)	15 (50)	<0.001
Age at diagnosis, years							
Mean±SD	2.9±4.7	4.3±5.4	4.3±5.6	1.1±2.8	14.2±5.8	6.3±6.3	<0.001
Median (IQR)	0.5 (0.1–3.6)	1.5 (0.3–6.9)	1.4 (0.5–5.8)	0.3 (0.0–0.6)	16.0 (14.8–17.1)	4.4 (0.4–12.1)	<0.001
Hispanic							0.24
Yes	235 (16)	115 (17)	8 (15)	108 (15)	1 (13)	3 (10)	
No/Unknown	1240 (84)	548 (73)	46 (85)	612 (85)	7 (88)	27 (90)	
Race group							<0.001
White	899 (61)	400 (60)	36 (67)	444 (62)	4 (50)	15 (50)	
Black	191 (13)	66 (10)	6 (11)	105 (15)	3 (38)	11 (37)	
Asian	135 (9)	84 (13)	3 (6)	45 (6)	0 (0)	3 (10)	
Other/Unknown	250 (17)	113 (17)	9 (17)	126 (18)	1 (13)	1 (3)	

Data are presented as n (%), unless otherwise stated; column percentages for each characteristic total 100%. UCSF: University of California San Francisco; CHOP: Children's Hospital of Philadelphia. The p-value tests equality of the distributions of each characteristic between Group 1 and Group 3 ($p<0.05$ is significant).

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TABLE 2

Diseases associated with paediatric pulmonary hypertension (PH) patients with World Symposium on Pulmonary Hypertension (WSPH) Groups 1, 1′ and 1″ as primary classification

Group 1: Pulmonary arterial hypertension (PAH)	602 (90.8)
1.1 Idiopathic	148 (22.3)
1.2 Heritable	40 (6.1)
1.3 Drug and toxins induced	2 (0.3)
1.4 Associated with PAH	410 (61.8)
1.4.1 Connective tissue disease	9 (1.4)
1.4.2 HIV infection	0 (0)
1.4.3 Portal hypertension	6 (0.9)
1.4.4 Congenital heart disease[#]	390 (58.8)
1.4.4.1 Type	312 (47.1)
1.4.4.1.1 Simple pre-tricuspid shunts	93 (14.0)
1.4.4.1.1.1 Atrial septal defect	78 (11.7)
1.4.4.1.1.2 Total or partial unobstructed anomalous pulmonary venous return	15 (2.3)
1.4.4.1.2 Simple post-tricuspid shunts	112 (16.9)
1.4.4.1.2.1 Ventricular septal defect	77 (11.6)
1.4.4.1.2.2 Patent ductus arteriosus	54 (8.1)
1.4.4.1.3 Combined shunts	35 (5.3)
1.4.4.1.4 Complex congenital heart disease	121 (18.2)
1.4.4.1.4.1 Complete atrioventricular septal defect	52 (7.8)
1.4.4.1.4.2 Truncus arteriosus	3 (0.5)
1.4.4.1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow	20 (3.0)
1.4.4.1.4.4 Transposition of the great arteries	16 (2.4)
1.4.4.2 Direction of shunt	99 (14.9)
1.4.4.2.1 Predominantly systemic-to-pulmonary	51 (7.7)
1.4.4.2.2 Predominantly pulmonary-to-systemic (Eisenmenger's)	27 (4.1)
1.4.4.2.3 Bidirectional	19 (2.9)
1.4.4.3 Repair status	170 (25.6)
1.4.4.3.1 Unoperated	43 (6.5)
1.4.4.3.2 Partial repair	18 (2.7)
1.4.4.3.3 Complete repair	109 (16.4)
1.4.5 Schistosomiasis	0 (0)
Group 1′: Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis	11 (1.7)
Group 1″: Persistent PH of the newborn	50 (7.6)

Data are presented as n (%); all percentages are based on WSPH Groups 1, 1′ and 1″ (n=663) as the denominator. Category counts may be larger than the sum of counts for associated subclasses, due to the classification of disease for some patients only at a high-level subgroup.

[#]: subclasses for congenital heart disease are not mutually exclusive, as more than one heart defect may be associated with a single patient.

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TABLE 3

Diseases associated with paediatric pulmonary hypertension (PH) with World Symposium on Pulmonary Hypertension (WSPH) Group 3 as the primary classification

Group 3: PH due to lung diseases and/or chronic hypoxia	718 (100)
3.1 Chronic obstructive pulmonary disease	4 (0.6)
3.2 Interstitial lung disease	29 (4.0)
3.2.1 Alveolar capillary dysplasia	3 (0.4)
3.2.2 Pulmonary interstitial glycogenosis	6 (0.8)
3.2.3 Surfactant protein deficiency	4 (0.6)
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern	13 (1.8)
3.4 Sleep disordered breathing	18 (2.5)
3.5 Alveolar hypoventilation disorders	3 (0.4)
3.6 Chronic exposure to high altitude	3 (0.4)
3.7 Developmental abnormalities	651 (90.4)
3.7.1 Bronchopulmonary dysplasia	320 (44.4)
3.7.2 Congenital cystic adenomatoid malformation	7 (1.0)
3.7.3 Congenital diaphragmatic hernia	256 (35.6)

Data are presented as n (%); all percentages are based on WSPH Group 3 (n=718) as the denominator. Subclasses may include overlapping or concurrent WSPH classifications.

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TABLE 4

Genetic findings reported as the primary World Symposium on Pulmonary Hypertension (WSPH) classification

Group 1: Pulmonary arterial hypertension (PAH)	
1.2 Heritable	40 (100)
1.2.1 *BMPR2*	17 (43)
1.2.2 *ALK1/ENG* (with or without hereditary haemorrhagic telangiectasia)	5 (13)
1.2.3 *SMAD9*	0 (0)
1.2.4 *CAV1*	1 (3)
1.2.5 *KCNK3*	1 (3)
1.2.6 Unknown	6 (15)
1.2.7 Other	10 (25)
TBX4	6 (15)
GDF2 mutation	2 (5)
Other/family history	2 (5)

Data are presented as n (%); all percentages are based WSPH Group 1.2 heritable disease (n=40) as the denominator.

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TABLE 5

Genetic syndromes associated with paediatric pulmonary hypertension

	Overall (n=1475)	WSPH group					p-value
		Group 1 (n=663)	Group 2 (n=54)	Group 3 (n=720)	Group 4 (n=8)	Group 5 (n=30)	
Down	158 (10.7)	116 (17.5)	2 (3.7)	33 (4.6)	0 (0)	7 (23.3)	<0.001
DiGeorge	21 (1.4)	15 (2.3)	1 (1.9)	5 (0.7)	0 (0)	0 (0)	0.015
Noonan	7 (0.5)	3 (0.5)	1 (1.9)	2 (0.3)	0 (0)	1 (3.3)	0.59
Russell-Silver	1 (0.1)	0 (0)	0 (0)	1 (0.1)	0 (0)	0 (0)	0.34
Trisomy 18	8 (0.6)	7 (1.1)	0 (0)	1 (0.1)	0 (0)	0 (0)	0.027
CHARGE	7 (0.5)	2 (0.3)	0 (0)	4 (0.6)	0 (0)	1 (3.3)	0.46
VACTERL	4 (0.3)	0 (0)	1 (1.9)	2 (0.3)	0 (0)	1 (3.3)	0.17
Scimitar	3 (0.2)	2 (0.3)	0 (0)	1 (0.1)	0 (0)	0 (0)	0.53
Prader-Willi	4 (0.3)	2 (0.3)	0 (0)	2 (0.3)	0 (0)	0 (0)	0.95
Other [#]	36 (2.4)						

Data are presented as n (%), unless otherwise stated; percentages represent the percentage of patients with the listed syndrome. WSPH: World Symposium on Pulmonary Hypertension.

[#]: other disorders are listed in supplementary table S1. The p-value tests equality of the percentage of patients with each syndrome in the Group 1 *versus* Group 3 cohorts (p<0.05 is significant).

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TABLE 6

Respiratory therapy and medications at time of enrolment for the entire cohort and by primary World Symposium on Pulmonary Hypertension (WSPH) group

	Overall (n=1475)	WSPH group#					p-value
		Group 1 (n=663)	Group 2 (n=54)	Group 3 (n=720)	Group 4 (n=8)	Group 5 (n=30)	
Median (IQR) time since PH diagnosis, years	1.3 (0.2–4.8)	1.6 (0.1–5.6)	0.8 (0–4.1)	1.2 (0.3–4.0)	0.2 (0–3.8)	1.1 (0.2–4.3)	0.45
Any respiratory treatment ¶	945 (64)	363 (55)	22 (41)	537 (75)	5 (63)	18 (60)	<0.001
On any PH medication	932 (63)	515 (78)	34 (63)	361 (50)	4 (50)	18 (60)	<0.001
CCB	71 (5)	46 (7)	1 (2)	19 (3)	0 (0)	5 (17)	<0.001
ERA	313 (21)	227 (34)	5 (9)	74 (10)	2 (25)	5 (17)	<0.001
PDE5 inhibitor	819 (56)	447 (68)	32 (59)	323 (45)	2 (25)	15 (50)	<0.001
Prostacyclin	232 (16)	180 (27)	5 (9)	46 (6)	0 (0)	1 (3)	<0.001
Inhaled nitric oxide	60 (4)	30 (5)	3 (6)	25 (4)	2 (25)	0 (0)	0.31
Selexipag	1 (0.1)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0.30
PH medications							<0.001
Monotherapy	526 (36)	226 (34)	23 (43)	263 (37)	3 (38)	11 (37)	
Combination	406 (28)	289 (44)	11 (20)	98 (14)	1 (14)	7 (23)	
None	542 (37)	147 (22)	20 (37)	359 (50)	4 (50)	12 (40)	
Monotherapy	526	226	23	263	3	11	0.005
CCB	29 (6)	16 (7)	1 (4)	10 (4)	0 (0)	2 (18)	
ERA	32 (6)	17 (8)	0 (0)	13 (5)	1 (33)	1 (9)	
PDE5 inhibitor	425 (81)	167 (74)	21 (91)	228 (87)	1 (33)	8 (73)	
Prostacyclin	18 (3)	13 (6)	1 (4)	4 (2)	0 (0)	0 (0)	
Inhaled nitric oxide	22 (4)	13 (6)	0 (0)	8 (3)	1 (33)	0 (0)	
Selexipag	0	0					
On any PH-associated medication	805 (55)	409 (62)	40 (74)	337 (47)	4 (50)	15 (50)	<0.001
PGE_1	13 (1)	2 (0.3)	0 (0)	11 (2)	0 (0)	0 (0)	0.018
Dopamine	34 (2)	15 (2)	1 (2)	18 (3)	0 (0)	0 (0)	0.78
Milrinone	32 (2)	13 (2)	1 (2)	18 (3)	0 (0)	0 (0)	0.50
Aspirin	144 (10)	103 (16)	15 (28)	24 (3)	0 (0)	2 (7)	<0.001
Coumadin	78 (5)	63 (10)	5 (9)	5 (0.7)	3 (38)	2 (7)	<0.001
Digoxin	91 (6)	59 (9)	9 (17)	21 (3)	0 (0)	2 (7)	<0.001
Diuretics	565 (38)	261 (39)	34 (63)	259 (36)	1 (13)	10 (33)	0.19
Iron supplement	155 (11)	55 (8)	4 (7)	94 (13)	0 (0)	2 (7)	0.003
Plavix	4 (0.3)	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0.037
Thyroid replacement	65 (4)	35 (5)	3 (6)	24 (3)	0 (0)	3 (10)	0.07

Data are presented as n (%), unless otherwise stated; percentages represent the percentage of patients prescribed the listed treatment within each WSPH group. IQR: interquartile range; PH: pulmonary hypertension; CCB: calcium channel blocker; ERA: endothelin receptor agonist; PDE5: phosphodiesterase type 5; PGE_1: PGE_1: prostaglandin E_1.

[#]: medications data were missing for n=1 patient in Group 1, and respiratory therapy data were missing for n=1 patient in Group 1 and n=1 patient in Group 3;

[¶]: respiratory treatments are defined as supplemental oxygen, airway medications and noninvasive or invasive respiratory support. The p-value reflects the comparison of the percentage of patients on each medication or tests equality of the distributions of the medication types for the Group 1 *versus* Group 3 cohorts ($p<0.05$ is significant).

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