Clinical features of paediatric pulmonary hypertension: a registry study

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Summary

Background Paediatric pulmonary hypertension, is an important cause of morbidity and mortality, and is insufficiently characterised in children. The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry is a global, prospective study designed to provide information about demographics, treatment, and outcomes in paediatric pulmonary hypertension.

Methods Consecutive patients aged 18 years or younger at diagnosis with pulmonary hypertension and increased pulmonary vascular resistance were enrolled in TOPP at 31 centres in 19 countries from Jan 31, 2008, to Feb 15, 2010. Patient and disease characteristics, including age at diagnosis and at enrolment, sex, ethnicity, presenting symptoms, pulmonary hypertension classification, comorbid disorders, medical and family history, haemodynamic indices, and functional class were recorded. Follow-up was decided by the patients' physicians according to the individual's health-care needs.

Findings 362 of 456 consecutive patients had confirmed pulmonary hypertension (defined as mean pulmonary artery pressure ≥25 mm Hg, pulmonary capillary wedge pressure ≤12 mm Hg, and pulmonary vascular resistance index ≥3 WU/m^{-2}). 317 (88%) patients had pulmonary arterial hypertension (PAH), which was idiopathic [IPAH] or familial [FPAH] in 182 (57%), and associated with other disorders in 135 (43%), of which 115 (85%) cases were associated with congenital heart disease. 42 patients (12%) had pulmonary hypertension associated with respiratory disease or hypoxaemia, with bronchopulmonary dysplasia most frequent. Finally, only three patients had either chronic thromboembolic pulmonary hypertension or miscellaneous causes of pulmonary hypertension. Chromosomal anomalies, mainly trisomy 21, were reported in 47 (13%) of patients with confirmed disease. Median age at diagnosis was 7 years (IQR 3–12); 59% (268 of 456) were female. Although dyspnoea and fatigue were the most frequent symptoms, syncope occurred in 31% (57 of 182) of patients with IPAH or FPAH and in 18% (eight of 45) of those with repaired congenital heart disease; no children with unrepaired congenital systemic-to-pulmonary shunts had syncope. Despite severe pulmonary hypertension, functional class was I or II in 230 of 362 (64%) patients, which is consistent with preserved right-heart function.

Interpretation TOPP identifies important clinical features specific to the care of paediatric pulmonary hypertension, which draw attention to the need for paediatric data rather than extrapolation from adult studies.

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See Online for webappendix

Introduction

Pulmonary hypertension with increased pulmonary vascular resistance is associated with substantial morbidity and mortality. The most recent clinical classification defines five pulmonary hypertension groups, with pulmonary arterial hypertension (PAH) being group 1 (the full classification is provided in the webappendix).[1] PAH can be idiopathic (IPAH), heritable (HPAH), or associated with conditions (APAH) such as congenital heart disease and can present at any age. It is a rare disease with incidence and prevalence estimates of 2–3 per million and 25–50 per million, respectively.

Without treatment, median survival after diagnosis of IPAH or HPAH has been reported as 2·8 years in adults, but survival in children might be worse.[2] Clinical trials and registries have led to substantial progress in treatment of this disorder in adults.[2–6] Although pathobiology and clinical features share similarities in children and adults, paediatric pulmonary hypertension could well differ from adult disease.[7–9] Adult studies alone cannot provide a basis for optimum care for children. However, paediatric pulmonary hypertension is insufficiently characterised. The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry is a global, prospective, observational study designed to provide information about demographics, course, treatment, and outcomes in paediatric pulmonary hypertension.[10]

Methods

Study design

TOPP is a centre-based, comprehensive registry, which was initiated on Jan 31, 2008. Enrolled patients undergo assessment, treatment, and follow-up according to the judgment of their physicians. No specific therapy or follow-up protocols are part of TOPP. Patients in clinical trials are eligible. Patients were enrolled from 31 centres in 19 countries in five continents (sites and investigators are listed at the end of the report). Patients with

pulmonary hypertension caused by left-heart disease (group 2) were excluded unless the left-heart disease had been corrected and the patient had persistent pulmonary hypertension with increased pulmonary vascular resistance at least a year post-repair and no residual left-sided disease.

The study was designed and supervised by the Executive Board of the Association for Pediatric Pulmonary Hypertension (Board members are listed at the end of the report). Data management and analyses were done by a contract organisation working with the Executive Board.

Study population

We prespecified diagnosis on or after Jan 1, 2001, to provide a population representative of present practice. To minimise selection bias, physicians at all sites screened all consecutive patients presenting with suspected or confirmed PAH or pulmonary hypertension groups 3–5 (classified according to the 2003 3rd World Pulmonary Hypertension Symposium[11]) with increased pulmonary vascular resistance. Patients aged between 3 months and 18 years at the time of diagnosis with PAH (group 1), pulmonary hypertension associated with respiratory disorders (group 3), chronic thromboembolic pulmonary hypertension (group 4), or miscellaneous causes of pulmonary hypertension (group 5) were eligible if they met the prespecified haemodynamic enrolment criteria: pulmonary hypertension, increased pulmonary vascular resistance, and normal left-sided filling pressures irrespective of pulmonary hypertension group.[11] We included both newly diagnosed patients (incident; diagnosis within 3 months of enrolment) and previously diagnosed patients (prevalent; diagnosis more than 3 months before enrolment).

According to the 2003 classification,[11] cases with familial aggregation of the disease were classified as familial PAH (FPAH), although the most recent classification would use HPAH.[1] Patients with congenital heart disease with left-sided obstruction and persistent pulmonary hypertension at least a year post repair (without residual obstruction—ie, mean pulmonary capillary wedge pressure [mPCWP] ≤12 mm Hg at ≥1 year post repair with right-heart catheterisation) were also eligible (included in group 1). We did not include pulmonary venous hypertension irrespective of pulmonary vascular resistance index (PVRi, classically defined group 2) because therapy for these patients is initially directed towards treating the left-sided heart disease. Patients with APAH associated with congenital heart disease were classified as having an open, clinically significant congenital systemic-to-pulmonary shunt (unrepaired or repaired but with a substantial residual shunt), a corrected (closed) congenital systemic-to-pulmonary shunt, or as congenital heart disease that had never been associated with a congenital systemic-to-pulmonary shunt.

The diagnosis of confirmed pulmonary hypertension required right-heart catheterisation with mean pulmonary arterial pressure (mPAP) 25 mm Hg or more, PVRi 3 WU/m^{-2} or more, and mPCWP 12 mm Hg or less. In cases in which right-heart catheterisation could not be done for specific clinical reasons (eg, patient died before scheduled procedure), patients could be considered for enrolment on the basis of confirmatory echocardiography or histopathology, or both, provided that the executive board, masked to site, validated the diagnosis and agreed with why the right-heart catheterisation was not done. All patients who met enrolment criteria were informed of the registry and were eligible to provide written informed consent to participate. Parental consent was obtained for patients younger than 18 years The protocol was approved by institutional review boards and ethics committees.

Patient follow-up and data collection

We obtained patient and disease characteristics, including age at diagnosis and at enrolment, sex, ethnicity, presenting symptoms, pulmonary hypertension classification, comorbid disorders, medical and family history, haemodynamic indices, and functional class with an electronic case record form. Follow-up was decided by the patients' physicians according to the individual's health-care needs. No visits were required, but consistent with standard practice, physicians were encouraged to schedule follow-up at least yearly. All patients will be followed up for at least 3 years.

Statistical methods and analysis

TOPP was designed to enrol about 450 patients. A priori, we decided that the sample population would include incident and prevalent patients. To ensure enrolment of a sufficient number of incident cases, a 2 to 1 ratio of prevalent to incident patients was prespecified with the ability to stop enrolment of prevalent patients once the two-thirds target was reached. Further, the protocol prespecified that enrolment of patients with PAH associated with congenital heart disease could be stopped, either at a specific site or at all sites, if the number of such patients exceeded 50% of the total target population. Last, to maximise the global generalisability of the data, patient enrolment at a particular site could be stopped to prevent overrepresentation of one site.

The statistical analysis plan was designed to meet the registry objectives and was finalised before we did any analyses. For the aims of this report, analyses are descriptive. The populations analysed were the all-patients cohort, and the confirmed pulmonary hypertension cohort, which included only patients who met all enrolment criteria. We summarised continuous data using standard descriptive statistics—mean, SD, 95% CIs, and median, minimum, maximum, 25th and 75th percentiles—when appropriate, and categorical data

using counts and percentages. The denominator for percentages was the total number of patients with no missing data for each variable analysed. Missing data were not imputed. We calculated 95% CIs using the normal approximation for the binomial distribution. We did not do a formal sample size calculation and hence the sample was not powered a priori for specific comparisons. For formal statistical analyses, we examined categorical data with χ^2 tests and continuous data using analysis of variance (ANOVA). The assumptions underlying the ANOVA were checked and appropriate non-parametric analyses done when the assumption of normality was in doubt. We used SAS statistical software package (version 8.2 or higher) for the analyses. The cutoff date for data inclusion was Feb 15, 2010.

Role of the funding source

The TOPP registry is supported by a research grant from Actelion Pharmaceuticals. Actelion does not participate in the management of the registry, nor does it have access to the database, the individual sites, or patient data. The sponsor had no role in study design, analysis, interpretation of data, writing of the manuscript, or the decision to submit the paper for publication. All decisions related to the registry lie solely with the executive board of the Association for Pediatric Pulmonary Hypertension. The executive board decided to submit the paper for publication and wrote the report with contributions from all authors. All authors had access to the data and analyses. The corresponding author had full access to all the data in

	All patients	Patients with confirmed pulmonary hypertension		
		All	Incident	Prevalent
Patients	456 (100%)	362 (79%)	102 (28%)	260 (72%)
Female	268 (59%)	214 (59%)	58 (57%)	156 (60%)
Preterm	63 (14%)	47 (13%)	16 (16%)	31 (12%)
Age at diagnosis (years)	7·1 (6·6–7·6)	7·5 (7·0–8·1)	8·5 (7·5–9·5)	7·2 (6·5–7·8)
Weight (kg)	26·5 (24·7–28·4)	28·0 (25·9–30·1)	30·8 (26·7–35·0)	26·8 (24·4–29·3)
Height (cm)	117 (114–120)	119 (116–123)	124 (118–131)	117 (113–121)
BMI (kg/m^2)	17·05 (16·63–17·48)	17·21 (16·74–17·68)	17·68 (16·67–18·69)	17·02 (16·50–17·54)
BSA (m^2)	0·93 (0·88–0·97)	0·94 (0·90–0·99)	1·02 (0·93–1·11)	0·91 (0·86–0·97)
Ethnicity	454 (100%)	362 (100%)	102 (100%)	260 (100)
White or Hispanic	302 (67%)	229 (63%)	57 (56%)	172 (66%)
Black	14 (3%)	8 (2%)	5 (5%)	3 (1%)
Asian	107 (24%)	99 (27%)	33 (32%)	66 (25%)
Other	15 (3%)	13 (4%)	5 (5%)	8 (3%)
Unknown	16 (4%)	13 (4%)	2 (2%)	11 (4%)
Time from onset symptoms to diagnosis (months)	17 (15–20)	17 (14–20)	24 (16–31)	15 (12–18)
Median (IQR)	6 (2–19)	6 (2–19)	6 (3–38)	5 (1–17)
Time from diagnosis to enrolment (months)	24·0 (21·7–26·4)	24·4 (21·8–27·1)	0·7 (0·5–0·9)	33·7 (30·7–36·7)
Median (range)	13·7 (1·7–39·8)	14·1 (2·3–39·8)	0·2 (0·0–1·1)	28·5 (12·6–48·9)
Group I*	398 (87%)	317 (88%)	88 (86%)	229 (88%)
IPAH or FPAH	212 (53%)	182 (57%)	55 (63%)	127 (55%)
APAH-congenital heart disease	160 (40%)	115 (36%)	26 (30%)	89 (39%)
Systemic-to-pulmonary shunt	150 (38%)	107 (34%)	25 (28%)	82 (36%)
Unrepaired	91 (23%)	61 (19%)	14 (16%)	47 (21%)
Repaired	57 (14%)	45 (14%)	10 (11%)	35 (15%)
Never shunt	12 (3%)	9 (3%)	2 (2%)	7 (3%)
Repaired left obstruction	7 (2%)	7 (2%)	1 (1%)	6 (3%)
APAH-connective tissue disease	10 (3%)	9 (3%)	1 (1%)	8 (3%)
APAH-chronic liver disease	4 (1%)	2 (1%)	0 (0%)	2 (1%)
APAH-HIV	0 (0%)	0 (0%)	0 (0%)	0 (0%)
APAH-drugs or toxins	0 (0%)	0 (0%)	0 (0%)	0 (0%)
APAH-HHT	2 (1%)	1 (<1%)	1 (1%)	0 (0%)
APAH-thyroid	2 (1%)	1 (<1%)	0 (0%)	1 (<1%)
APAH-other	3 (1%)	3 (1%)	0 (0%)	3 (1%)
PVOD or PCH	6 (2%)	6 (2%)	4 (5%)	2 (1%)
None of the above	5 (1%)	3 (1%)	2 (2%)	1 (<1%)

(Continues on next page)

	All patients	Patients with confirmed pulmonary hypertension		
		All	Incident	Prevalent
(Continued from previous page)				
Group 3*	52 (11%)	42 (12%)	13 (13%)	29 (11%)
Bronchopulmonary dysplasia	17 (33%)	11 (26%)	3 (23%)	8 (28%)
Interstititial lung disease	12 (23%)	10 (24%)	4 (31%)	6 (21%)
High altitude	7 (13%)	7 (17%)	3 (23%)	4 (14%)
Congenital diaphragmatic hernia	6 (12%)	4 (10%)	1 (8%)	3 (10%)
Congenital pulmonary hypoplasia	7 (13%)	5 (12%)	2 (15%)	3 (10%)
Disordered breathing or OSAS	5 (10%)	5 (12%)	0 (0%)	5 (17%)
Kyphoscoliosis	2 (4%)	2 (5%)	0 (0%)	2 (7%)
Other	2 (4%)	2 (5%)	1 (8%)	1 (3%)
Groups 4 or 5*	4 (1%)	3 (1%)	1 (1%)	2 (1%)
WHO Functional Class	449 (98%)	362 (100%)	102 (100%)	260 (100%)
I	54 (12%)	45 (12%)	11 (11%)	34 (13%)
II	212 (47%)	185 (51%)	52 (51%)	133 (51%)
III	146 (33%)	108 (30%)	28 (27%)	80 (31%)
IV	37 (8%)	24 (7%)	11 (11%)	13 (5%)
6 min walk test	175 (38%)	153 (42%)	46 (45%)	107 (41%)
Metres (mean [95% CI])	407 (389–426)	417 (398–436)	445 (414–476)	405 (381–429)

Data are n (%) or mean (95% CI) unless otherwise specified. Incident cases were those diagnosed within 3 months of enrolment. Prevalent cases were those diagnosed more than 3 months before enrolment. Two patients are missing for pulmonary hypertension classification because of missing data. Patients could be counted in more than one APAH disease category and in more than one associated disease category for group 3. BMI=body-mass index. BSA=body surface area. IPAH=idiopathic pulmonary arterial hypertension. FPAH=familial pulmonary arterial hypertension. APAH=pulmonary arterial hypertension associated with other disorders. HHT=hereditary haemorrhagic teleangiectasia. PVOD=pulmonary veno-occlusive disease. PCH=pulmonary capillary haemangiomatosis. OSAS=obstructive sleep apnoea syndrome. *Classified according to (3rd World Pulmonary Hypertension Symposium[11]).

Table 1: **Demographic and clinical characteristics at diagnosis in all patients and in patients with confirmed pulmonary hypertension**

the study and had final responsibility for the decision to submit for publication.

Results

From Jan 31, 2008, to Feb 15, 2010, 456 patients were enrolled. Enrolment of prevalent and incident patients was stopped at one site on Feb 10 and Aug 19, of 2009, respectively, to prevent overrepresentation of that site. Enrolment of prevalent patients at all other sites was stopped on May 22, 2009, to prevent such patients accounting for more than two-thirds of the total. No further predefined restriction rules were required.

Of the 456 patients in the all-patients cohort, 362 (79%) met all enrolment criteria for confirmed pulmonary hypertension, with 357 (99%) diagnoses based on right-heart catheterisation and five (1%) based on independently reviewed echocardiography and clinical records—of these five cases, three were further confirmed by histopathological findings. Of the confirmed pulmonary hypertension cases, about 30% were incident and about 70% were prevalent (table 1). The distribution of the all-patients cohort (456) was: Europe 157, Turkey 33, China 70, Japan 14, Australia 15, Brazil one, Mexico 21, USA 135, Canada ten. Of the 94 patients excluded from the confirmed pulmonary hypertension cohort, 11 did not meet haemodynamic criteria (six with mPAP<25 mm Hg or PVRI<3 WU/m^{-2}; five with mPCWP>12 mm Hg), and 83 did not have sufficient data to adequately calculate PVRi. Table 1 shows patient characteristics of each cohort. We recorded no apparent differences between patients in the confirmed pulmonary hypertension cohort and those excluded from that cohort.

In those with confirmed disease, the median age at diagnostic right-heart catheterisation was 7·0 years (IQR 3–12) with 61 patients (17%) diagnosed between 3 and 24 months of age, 111 (31%) between 2 and 6 years, 89 (25%) between 7 and 11 years, and 101 (28%) between 12 and 18 years. The average time from diagnostic right-heart catheterisation to enrolment was about 34 months in prevalent cases, and less than a month in incident cases (table 1). The mean time from onset of symptoms to diagnosis did not seem to differ between incident and prevalent cases, but tended to be longer when PAH was associated with congenital heart disease with unrepaired or residual systemic-to-pulmonary shunt and shorter in APAH not associated with congenital heart disease than in other subgroups (table 2).

PAH (group 1) and pulmonary hypertension associated with respiratory disorders or hypoxaemia (group 3) made up 88% (317) and 12% (42), respectively, of the confirmed pulmonary hypertension cohort (362). Only three patients (<1%) were in pulmonary hypertension group 4 or 5. There was an overall female preponderance (1·4 to 1) that was unchanged when stratified by incident or prevalent

case, pulmonary hypertension group, PAH subgroup, or age. Of the 317 PAH patients, 57% had IPAH or FPAH and 36% had APAH associated with congenital heart disease (table 2). Most congenital heart disease cases (106 out 115, 93%) included systemic-to-pulmonary shunts. APAH associated with disorders other than congenital heart disease was reported in 6% of PAH patients (table 2). Bronchopulmonary dysplasia was the most frequent disorder associated with pulmonary hypertension group 3, present in 11 of 42 patients (26%). We recorded a significant association between the number of patients in each pulmonary hypertension group and age (p=0·01), with pulmonary hypertension group 3 disorders occurring more frequently in patients aged 3–24 months at diagnosis than in older age-at-diagnosis cohorts (15 aged 3–24 months, 25%; 12 aged 2–6 years, 11%; six aged 7–11 years, 7%; and nine aged 12–18 years, 9%).

We recorded comorbid disorders in 86 of 362 (24%) patients with confirmed pulmonary hypertension. Chromosomal disorder was most frequent (47, 13%) with 42 patients having trisomy 21. There was a significant association between trisomy 21 and pulmonary hypertension group (p=0·02). Trisomy 21 was present more often in patients with group 3 disorders (nine of 42, 21%) than in those with PAH (group 1, 32 of 317, 10%). Within the PAH cohort (317), trisomy 21 was present in 26 of 115 (23%) patients with APAH associated with congenital heart disease, five of 182 (3%) patients with IPAH or FPAH, and one of 20 (5%) patients with APAH not associated with congenital heart disease. In the remaining 44 patients, we recorded a spectrum of other chromosomal abnormalities, syndromes, and non-chromosomal anomalies.

Of the 362 patients with confirmed pulmonary hypertension, 21 (6%) had lived at an altitude greater than 2000 m for more than 6 months, 47 (13%) were premature (gestation <37 weeks), and eight (2%) had a history of persistent pulmonary hypertension of the newborn. In five of these eight, pulmonary hypertension seemed to persist and was confirmed by right-heart catheterisation (done at >3 months of age), whereas in the other three, the disorder was thought to have resolved during the neonatal

	All PH confirmed	PH group 3	PH group 1					
			IPAH or FPAH	APAH with CHD				APAH excluding APAH with CHD
				All CHD	Unrepaired shunt*	Repaired shunt	Never shunt	
Patients	362 (100%)	42 (100%)	182 (100%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	20 (100%)
Female	214 (59%)	26 (62%)	109 (60%)	66 (57%)	38 (62%)	25 (56%)	3 (33%)	11 (55%)
Preterm	47 (13%)	18 (43%)	14 (8%)	11 (10%)	5 (8%)	6 (13%)	0 (0%%)	4 (20%)
Age at diagnosis (years) (mean [95% CI])	7·5 (7·0–8·1)	5·5 (3·7–7·3)	7·6 (6·9–8·3)	7·7 (6·7–8·8)	8·4 (6·9–9·9)	7·4 (5·8–8·9)	4·8 (0·6–9·0)	10·0 (7·5–12·4)
Incident patients	102 (28%)	13 (31%)	55 (30%)	26 (23%)	14 (23%)	10 (22%)	2 (22%)	7 (35%)
Ethnicity	362 (100)	42 (100)	182 (100)	115 (100)	61 (100)	45 (100)	9 (100)	20 (100)
White or Hispanic	229 (63%)	35 (83%)	118 (65%)	65 (57%)	35 (57%)	28 (62%)	2 (22%)	8 (40%)
Black	8 (2%)	0 (0%)	5 (3%)	2 (2%)	2 (3%)	0 (0%)	0 (0%)	1 (5%)
Asian	99 (27%)	3 (7%)	48 (26%)	40 (35%)	23 (38%)	12 (27%)	5 (56%)	8 (40%)
Other	13 (4%)	2 (5%)	5 (3%)	3 (3%)	1 (2%)	2 (4%)	0 (0%)	3 (15%)
Unknown	13 (4%)	2 (5%)	6 (3%)	5 (4%)	0	3 (7%)	2 (22%)	0 (0%)
Time from onset symptoms to diagnosis (months) (mean [95% CI])	17 (14–20)	16 (7–25)	15 (11–19)	24 (17–32)	30 (16–44)	19 (11–26)	22 (4–40)	5 (1–8)
Median (IQR)	6 (2–19)	4 (1–20)	5 (1–17)	9 (4–29)	10 (3–28)	8 (4–25)	9 (7–45)	3 (1–4)
Time from diagnosis to enrolment (months) (mean [95% CI])	24 (22–27)	25 (18–32)	25 (21–29)	24 (19–28)	23 (16–29)	25 (18–32)	24 (3–46)	16 (6–27)
Median (IQR)	14 (2–40)	22 (2–40)	15 (1–43)	14 (4–41)	13 (4–36)	19 (6–45)	20 (4–26)	8 (1–23)
WHO functional class	362 (100%)	42 (100%)	182 (100%)	115 (100%)	61 (100%)	45 (100%)	9 (100%)	20 (100%)
I	45 (12%)	8 (19%)	28 (15%)	8 (7%)	2 (3%)	4 (9%)	2 (22%)	1 (5%)
II	185 (51%)	20 (48%)	84 (46%)	72 (63%)	40 (66%)	28 (62%)	4 (44%)	8 (40%)
III	108 (30%)	13 (31%)	55 (30%)	31 (27%)	18 (30%)	13 (29%)	0 (0%)	7 (35%)
IV	24 (7%)	1 (2%)	15 (8%)	4 (3%)	1 (2%)	0 (0%)	3 (33%)	4 (20%)
6 min walk test	153 (42%)	10 (24%)	83 (46%)	50 (43%)	30 (49%)	19 (42%)	1 (11%)	9 (45%)
Metres (mean [95% CI])	417 (398–436)	466 (352–580)	407 (379–434)	422 (393–452)	420 (385–456)	429 (370–488)	355 (NC)	427 (330–525)

Patients from pulmonary hypertension groups 4 and 5 (n=3), included in all patients with confirmed pulmonary hypertension, are not depicted separately in this table. APAH=pulmonary arterial hypertension associated with other disorders. IPAH=idiopathic pulmonary arterial hypertension. FPAH=familial pulmonary arterial hypertension. CHD=congenital heart disease. NC=not calculated. *Or partial repair.

***Table 2*: Demographic and clinical characteristics at diagnosis in patients with confirmed pulmonary hypertension (PH confirmed) diagnosis according to pulmonary hypertension groups and subgroups**

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