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Epidemiology of Pulmonary Arterial Hypertension

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Abstract The epidemiology of pulmonary arterial hypertension (PAH) has changed over the last decade. Remarkable advances in understanding the pathobiology and clinical care required in PAH have resulted in improved quality of life and survival. Despite such important progress, the long-term rate of survival is still unacceptable. The epidemiology of PAH could not be easily generalized globally, due to the fact that nearly all of the present data has been gathered from Western, multicenter, prospective registries. There are potentially marked differences in PAH patients from Western and Eastern populations, and from developed and developing countries. Therefore, it is clear that more registry data will be needed to address novel questions emerging with improved knowledge of PAH.

Keywords Pulmonary arterial hypertension · PAH · Epidemiology · Prognosis · Heritable PAH · Connective tissue disease · Congenital heart disease · CHD · Human immunodeficiency virus · HIV · Portopulmonary hypertension · PoPH · Drugs · Toxins · Schistosomiasis · Pulmonary veno-occlusive disease · PVOD

Introduction

The consequences of pulmonary arterial hypertension (PAH), although variable with respect to time course and disease progression, are progressive right heart failure and death, if left untreated [1]. However, in the past two decades, significant advances made in our understanding of its pathobiology have led to exciting developments in therapeutic strategies [2–4•]. Although pulmonary vascular disease is associated with various etiologies, based on similarities in clinical presentation, pathology and mechanistic abnormalities in the pulmonary circulation, similar therapies for PAH appear to be safe and efficacious in many PAH patients, regardless of the underlying associated condition. With these therapeutic developments, despite an inability to "cure" the pulmonary vascular disease, currently available treatment options have significantly improved the overall quality of life and outcome for many PAH patients [5••].

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Overview of PAH Registries

In rare diseases such as PAH, registries provide valuable information on the baseline characteristics and outcomes of the disease. The characteristics of six major registries organized in last decade are shown in Tables 1 and 2.

The US National Institutes of Health (NIH) registry was started in 1981, and the results were published in 1987 [6••, 7••]. There were 187 patients with primary pulmonary hypertension (now called idiopathic pulmonary arterial hypertension, IPAH), with a mean age of 36 years and a female/male ratio of 1.7:1. From this benchmark study, it was concluded that the annual incidence of primary PH was 1–2 cases per million people. Furthermore, an exceedingly poor long-term prognosis and a median survival of 2.8 years after diagnosis were observed.

The French national registry collected the records of patients from 17 centers in France during the period of October 2002 to October 2003 [8••]. A total of 674 patients were entered into the database. The calculated total prevalence and annual incidence of PAH were 15 and 2.4 cases per million in the population, respectively. Idiopathic, familial, anorexigen, connective tissue diseases (CTD), congenital

Table 1 General Information from PAH Registries Conducted in the Past 10 Years from Different Countries

	Study cohort	Study design and time period	No. of Patients	Incidence/prevalence
French	Group 1 PH Age >18 yrs	Prospective; 2002-2003	674	PAH 2.4/15 cases/ MAI IPAH 1.0/5.9 cases/MAI
US-REVEAL	Group 1 PH	Prospective; 2006-2009	3515 (Age >3 months)	PAH 2.0/10.6 cases/ MAI IPAH 0.9 cases/MAI
Spanish	Group 1 PH and CTEPH Age >14 yrs	Retrospective; 1998-2006 Prospective; 2007-2008	PAH 866 CTEPH 162	PAH 3.2/16 cases/ MAI IPAH 1.2/4.6 cases/MAI
UK	IPAH, HPAH and Anorexigen-associated PAH	Prospective; 2001-2009	482	1.1/6.6 cases/MI
COMPARE Registry	IPAH Age >18 yrs	Prospective, 2007-2011	587	NA
New Chinese Registry	Group 1 PH Age >18 yrs	Prospective; 2008-2011	956	NA

CHD congenital heart disease, *CTD* connective tissue disease, *CTEPH* chronic thromboembolic pulmonary hypertension, *HPAH* heritable pulmonary arterial hypertension, *IPAH* idiopathic pulmonary arterial hypertension, *MAI* million adult inhabitants, *MI* million inhabitants, *NA* not available, *PAH* pulmonary arterial hypertension, *PHC* Pulmonary hypertension connection, *SMR* Scottish morbidity record

heart diseases (CHD), portal hypertension, and HIV-associated PAH accounted for 39.2, 3.9, 9.5, 15.3, 11.3, 10.4, and 6.2 % of the population, respectively. The mean age of patients with IPAH at diagnosis was 52 years in the French cohort, much older than in the 1980s as reported for the NIH registry. Accordingly, more elderly patients that were older than age 65 were diagnosed with IPAH in the French registry. However, a significant delay from the symptom onset to the diagnostic right heart catheterization (RHC) in patients with PAH was still noted, despite the huge improvements in public awareness and diagnostic techniques that have been achieved in the last two decades. As a result, 80 % of IPAH patients had WHO functional class III or IV symptoms at the time of diagnosis in the French cohort. In the cohort of whole PAH patients, 1-, 2-, and 3-year survival rates were 87, 76, and 67 %, respectively [9•]. In prevalent idiopathic, familial and anorexigen-associated PAH, 1-, 2-, and 3-year survival rates were higher than in incident patients. The survival bias revealed here strongly suggests that analysis of incident cohorts of homogeneous PAH populations should be recommended in the future. Further analysis demonstrated that idiopathic, familial, and anorexigen-associated types of PAH each represent a progressive, fatal disease with a 3-year survival of only 54.9 % [10•]. Mortality is most closely associated with male gender, right ventricular hemodynamic function, and exercise limitation.

Table 2 Demographic Characteristics of PAH Registries Conducted in the Past 10 Years from Different Countries

	Age, yrs		Female, %		WHO III/IV, %	
	PAH	IPAH	PAH	IPAH	PAH	IPAH
French	50±15	52±15	65	62	75	81
US-REVEAL	50±14	50±15	80	83	56	55
Spanish	45±17	46±18	71	73	69	70
UK	NA	50±17	NA	70	NA	84
EU-COMPARE	NA	65±15	NA	60	NA	91
New Chinese Registry	36±13	38±13	70	70	54	66

More recently, a multicenter registry (54 US sites), the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), was initiated to characterize the demographics, clinical course, hemodynamic features, and disease management of a US patient population with WHO group 1 PAH [11•, 12]. Overall, 2,525 adult PAH patients met the traditional hemodynamic criteria (mean pulmonary arterial pressure ≥25 mm Hg and pulmonary capillary wedge pressure ≤15 mm Hg) were recruited from March 2006 to September 2007 in the REVEAL registry. The low estimate for incidence of adult IPAH or FPAH and group 1 PAH in the United States based on REVEAL were 0.9 and 2.0 cases per million, respectively. The low estimates for adult prevalence for group 1 PAH was 10.6 cases per million. These numbers, despite the recognition that not all patients with PAH are included in REVEAL, provide a very conservative and carefully case-ascertained baseline for future evaluations of incidence and prevalence of PAH in the United States, against which future demographic studies can be compared. In the REVEAL registry, IPAH also was the leading cause, account for 46.2 % of whole group I PAH. The baseline data for PAH patients in the REVEAL registry were broadly similar to the French data. The mean ages of whole group 1 PAH and IPAH at diagnosis were 50±14 years and 50±15 years, respectively. The diagnostic age >65 years accounted for 16.7 % of patients with IPAH. The female preponderance was confirmed by the female-to-male ratio in both group I PAH (3.87:1) and IPAH (4.08:1). In the REVEAL population, a significant delay from

symptom onset to diagnosis still existed; the median duration was 24.9 months in group I PAH and 26.7 months in IPAH, respectively. As a result, the majority of patients at diagnosis had a severely impaired WHO/NYHA functional class (55.6 % of patients in Class III or IV) and markedly limited exercise capacity (mean 6-minute walk distance, 366±126 meters). Considerable improvements in survival were obtained in the REVEAL registry, with 1-, 3-, 5-, and 7-year survival rates from the time of diagnostic right-sided heart catheterization of 85, 68, 57, and 49 %, respectively. For patients with idiopathic/familial PAH, survival rates were 91, 74, 65,and 59 %, compared with estimated survival rates of 68, 47, 36, and 32 %, respectively, using the NIH equation [13].

In 2012, Escribano and colleagues reported PAH and CTEPH registry in Spain [14]. From 1998 to 2006, patients were recruited retrospectively, and from July 1st 2007 to June 30th 2008, recruited prospectively. Among 866 patients in the group with IPAH, the mean age was 45±17 years and the female-to-male ratio was 2.45. The mean duration of delay from symptom onset to diagnosis was 3.5±6.1 years; as a consequence, 69 % of patients were already Class III or IV at diagnosis. IPAH was also the leading cause of the whole PAH cohort. The reported 1-, 3- and 5-year survival rates for the whole IPAH cohort were 89, 77 and 68 %, respectively.

In the same year, Ling and colleagues presented recent information in the UK and Ireland [15]. They performed this longitudinal observational registry to prospectively identify those treatment-naive, incident cases of idiopathic, heritable and anorexigen-associated PAH diagnosed between 1st January 2001 and 31st December 2009 in all eight PH centers in the UK and Ireland. The registry showed changing demographics, epidemiology and survival rates of incident PAH compared with NIH data. A total of 482 patients (93 % idiopathic, 5 % heritable and 2 % anorexigen-associated PAH) were diagnosed, giving rise to an estimated incidence of 1.1 cases/million/year and prevalence of 6.6 cases/million in 2009. Patients enrolled in this registry were older (median age 50 years), with more cardiovascular comorbidities and better survival in the most recent era. A total of 129 patients died over the study period, with observed 1-, 2-, 3- and 5-year survival rates of 92.7, 84.0, 73.3 and 61.1 %, respectively. Younger patients (age ≤50) had shorter duration of symptoms, fewer comorbidities, better functional and exercise capacity, higher % DLCO, and more severe haemodynamic impairment, but better survival compared with older patients. In comparison with the earlier cohorts, patients diagnosed in 2007-9 were older, more obese, had lower % DLCO, and more comorbidities, but better survival rates.

In 2013, Hoeper and colleagues reported the preliminary demographic results from the COMPARE registry (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), a European-based registry on medical therapies for PH [16]. From June 2007 to November 2011, a total of 2,654 patients with PH had been enrolled into the COMPERA registry (87 % by German centers). IPAH was the leading etiology, accounting for 65.6 % of the PAH population. In 587 patients with incident IPAH studied for further analysis, the median diagnostic age was 71 years; and 202 patients were younger (18 –65 years) group and 378 were older (> 65 years) group. The female-to-male ratio was 2.3:1 in the younger patients, and 1.2:1 in the older ones. At the time of diagnosis, the younger patients presented more often in functional Class II, whereas older patients presented more often in functional Class IV. In accordance, the baseline 6MWD was significantly lower in the older patient group. Data from cardiac catheterization at baseline did show that PCWP was higher and mPAP and pulmonary vascular resistance (PVR) were lower in the older patient population, and that there was a trend towards lower mPAP values with increasing age. The long-term rates of survival after the diagnosis of IPAH were lower in elderly patients, even when adjusted for age- and gender-matched survival tables of the general population (the 1-, 2-, and 3-year survival rates in younger patients were 96.0, 90.9 and 83.3 % , respectively; the corresponding survival rates in the older patients were 89.8, 78.6 and 68.0 %).

The Problems of Current Registries

In some of the earlier registries, definition and assessment of PAH were not standardized, the numbers were small and a significant number of patients did not have right heart catheterization to confirm the diagnosis. In addition, most pulmonary hypertension (PH) registries were composed of a mixture of incident and prevalent patients. However, prevalent patients have a better prognosis compared with incident patients. It is concerning that the current knowledge of PAH based on data obtained from a mixed population may be biased. Patients with severe or rapidly progressive disease may die early and never live long enough to be enrolled in registries. Conversely, patients with stable disease for a number of years have better survival and may be over-represented in registries. In addition, patients outside participating centers were not included, potentially introducing further selection bias. The survival data of PAH in recent Western registries are listed in Table 3.

Epidemiologic Information in Different Etiologies

Heritable PAH

The cause of PAH is heterogeneous, and some cases are familial. A genetic basis for the development of PAH has been suspected since a family of patients with IPAH was described by Dresdale et al [17]. Loyd and Newman showed that

Table 3 Survival Data of PAH Registries Conducted in the Past 10 Years from Different Countries and Time Periods

	Study cohort	1 yrs, %		2 yrs, %		3 yrs, %		5 yrs, %	
		PAH	IPAH	PAH	IPAH	PAH	IPAH	PAH	IPAH
US-NIH	Inc	NA	68	NA	NA	NA	48	NA	34
French	Prev and Inc	Ent 87 Prev 88 Inc 88	Ent 83 Prev 89 Inc 89	Ent 76 Prev 79 Inc 65	Ent 67 Prev 77 Inc 68	Ent 67 Prev 71 Inc 51	Ent 58 Prev 69 Inc 55	NA	NA
US-REVEAL	Prev and Inc	85	91	NA	NA	68	74	57	65
Spanish	Prev and Inc	NA	89	NA	NA	NA	77	NA	68
UK	Inc	79[a]	93	68[a]	84	57[a]	73	NA	61
EU-COMPARE	Inc	NA	Ent 92 ≤65 y 96 >65 y 90	NA	Ent 83 ≤65 y 91 >65 y 79	NA	Ent 74 ≤65 y 83 >65 y 68	NA	NA

Inc Incident or newly diagnosed patients, *Prev* Prevalent or previously diagnosed patients, *Ent* Entire study population

[a] Survival data calculated only from patients with IPAH and patients with CTD-PAH

familial PAH has an autosomal dominant pattern of inheritance, an increased tendency for female carriers to manifest clinical disease [18, 19]. In 1997, linkage analysis in affected families allowed Nichols et al. [20••] and Morse et al. [21••] to localize on chromosome 2 the locus implicated in PAH development. Candidate genes in this region were then identified and mutations in the *BMPR2* (bone morphogenetic protein receptor type 2) gene were found in PAH patients [22, 23]. In the literature, a *BMPR2* mutation is detected in 58–74 % of PAH patients with a family history of the disease, and in 3.5–40 % of patients with so-called IPAH [24, 25•, 26–29].

PAH may also occur in patients carrying mutations in the gene encoding activin receptor–like kinase 1 (*ALK1 or ACVRL1*) and more rarely in patients carrying mutations in the gene encoding endoglin (*ENG*); mutations in both genes are known to cause hereditary hemorrhagic telangiectasia [30–33].

In rare cases, mutations in the gene that encodes mothers against decapentaplegic homologue 8 (*SMAD8*) have been identified in patients with IPAH [34]. Recently, other novel mutations in the gene encoding caveolin 1 (*CAV1*) have been identified in patients with either FPAH or IPAH [35]. However, in approximately 25 % of patients with FPAH, there is no identifiable genetic cause. More recently, six novel heterozygous missense variants in *KCNK3* (the gene encoding potassium channel subfamily K, member 3) were confirmed as disease-causing candidate genes in the family [36•]. Electrophysiological studies of the channel indicated that all these missense mutations resulted in a reduction of the potassium-channel current, which was successfully remedied by pharmacologic manipulation. This study suggested that PAH might be another potential channelopathy.

The analysis of clinical, functional, and hemodynamic characteristics of PAH patients indicates that PAH patients carrying a *BMPR2* mutation develop the disease 10 years earlier than noncarriers and have a more severe hemodynamic compromise at diagnosis [25•, 26, 30]. Moreover, a trend for more severe prognosis of the disease in males was observed, and particularly in those carrying a *BMPR2* mutation [10•, 37]. The analysis of clinical, functional, and hemodynamic characteristics of PAH patients carrying an *ALK1* mutation indicates that these patients are significantly younger at PAH diagnosis as compared with PAH patients carrying a *BMPR2* mutation and PAH patients without identified mutation [30]. PAH patients carrying an *ALK1* mutation have better hemodynamic status at diagnosis than *BMPR2* mutation carriers, but have shorter survival when compared with other patients despite similar treatment, suggesting a more rapid disease progression in *ALK1* mutation carriers [30].

Connective Tissue Disease

Connective tissue diseases (CTD) are commonly complicated by PAH, which is often the leading cause of death in this population. In recent Western PAH registries, CTD associated with PAH (CTD-PAH) accounted for 15.3–25.3 % in WHO Group 1 PAH population [8••, 11•, 16]. Among CTD-PAH, systemic scleroderma (SSc) is the most common cause, accounting for approximately 70 % in this sub-population, especially in patients with limited disease or the CREST syndrome [8••, 11•, 16, 38•]. Using strictly right heart catheterization (RHC) for the diagnosis of PAH, the prevalence of SSc-PAH in prospective studies is between 7.8 and 12 % [39–41], with variations probably dependent on referral biases.

Even when similar therapies are used, the survival of patients with PAH associated with SSc is less favorable than for patients with other forms of CTD [38•, 42•], or even worse than patients with IPAH [43]. Despite substantial improvements in other PAH categories, the figures remain sobering for

these patients with a 3-year survival rate well below 60 % [38•, 44, 45].

PAH also occurs in patients with other forms of CTD, including systemic lupus erythematosis (SLE), Sjögren's, mixed connective tissue disease (MCTD), rheumatoid arthritis (RA), polymyositis, dermatomyositis and other rare causes.

SLE

The exact prevalence of PAH in SLE remains unclear, but is likely less than in SSc, affecting about 0.5–14 % of patients based on a review of the literature encompassing over 100 patients [46–48]. The estimated prevalence range is wide, caused by multiple factors such as varied population groups, lack of a uniform PAH definition, and different diagnostic approaches (echocardiogram versus RHC). In a large community-based lupus cohort from the United Kingdom, the prevalence of SLE associated with PAH was 4.2 %. However, the UK study used echocardiograms, which tend to yield estimated systolic pulmonary artery pressures that can differ significantly from the "gold standard", RHC [48]. SLE accounted for 8 and 17 % in CTD-PAH in the United Kingdom and in the REVEAL registry, respectively [38•, 42•]. However, due to ethnic and geographical differences, SLE instead of SSc is the most common etiology related to PAH in Asia [49]. Most recently, two new registries initiated in China (180 patients with CTD-PAH diagnosed by right heart catheterization) [50••] and Korea (321 patients with CTD-PAH diagnosed by echocardiography) [51] both demonstrated that SLE was the leading underlying disease, accounting for 51.1 and 35.3 % in the CTD-PAH population, respectively, while SSc only accounted for 8.9 and 28.3 % in the two registries, respectively. The ethnic background is the most possible explanation for those differences. The patients with SLE-PAH are predominantly female (90 %), young (average age of 33 years at the time of diagnosis), and often suffer from Raynaud's phenomenon. Survival is now estimated at 78_94 % and 74 % at 1 and 3 years, respectively [38•, 42•]. This is clearly significantly better than SSc-PAH.

MCTD

MCTD is a separate entity among the CTDs, linked to anti-U1RNP antibodies. Most recently, a nationwide multicenter registry performed in Norway demonstrated that the prevalence of PH in MCTD was only 3.4 % [52]. The syndrome may occasionally respond to immunosuppressive drugs [53] and, therefore, these patients appear to have a better prognosis overall, compared with SSc-PAH patients with an estimated 2- and 3-year survival of 89 and 63 %, respectively [38•].

RA

PAH is a rare complication of rheumatoid arthritis and both the prevalence and impact of PH in these patients is not well-known. The 2- and 3-year estimated survival in these patients is 83 and 66 %, respectively [38•].

Primary Sjögren's Syndrome

Although primary Sjögren's syndrome is a fairly common autoimmune disease with glandular and extraglandular manifestations, it is very rarely complicated by PAH. In a recent review by LAUNAY et al. [54] of 28 well-characterized patients with primary Sjögren's syndrome and PAH, the mean age at diagnosis of PAH of these almost exclusively female patients (27 out of 28 patients) was 50 years. Standard therapy was typically ineffective despite an initial improvement. Survival rate was low (66 % at 3 years) [54].

Other forms of CTDs are very rarely complicated by PAH and the epidemiologic data have not been established. However, due to the diversity of epidemiology data of different CTDs in different regions and races, the predominant forms of CTDs with PAH might be varied significantly.

Congenital Heart Disease (CHD)

PAH is a frequent complication of CHD, particularly in patients with left-to-right (systemic-to-pulmonary) shunts. Persistent exposure of the pulmonary vasculature to increased blood flow and pressure may result in vascular remodeling and dysfunction. This leads to increased pulmonary vascular resistance (PVR) and, ultimately, to reversal of the shunt and development of Eisenmenger's syndrome.

In children, the predominant diagnoses of PAH are idiopathic and associated with CHD and shunt lesions [55, 56••]. Eisenmenger's syndrome is rarely seen in developed countries nowadays because of early diagnosis and surgical or interventional repair. Nevertheless, because of insufficient access to specialized care and late referral of patients in developing countries, CHD is still one of the most common etiologies of PAH worldwide.

The estimated prevalence of CHD is approximately 6–10 per 1,000 live births and overall 5–10 % of patients with CHD and as many as 30 % of unrepaired patients have PAH [57]. A diagnosis of PAH has ramifications for both pediatric and adult CHD patients. In children, the course of CHD is complicated by the presence of PAH: estimates suggest that approximately one-third of pediatric CHD patients develop significant PAH without early surgical repair [58]. However, the demographics of CHD are changing over the past few decades due to advances in the diagnosis, management and treatment of CHD. Increasing numbers of adults are presenting with

CHD, illustrated by the fact that there are 1.2 million adult CHD patients in Europe alone, all who are at risk of developing PAH.

In the US-REVEAL registry and French National Registry of PAH, PAH-CHD was the second most commonly associated form of PAH (after CTD-PAH) [8••, 9•, 16]. The prevalence of PAH associated with CHD (PAH-CHD) was calculated as 4.2 % among a population of 5,970 CHD patients included in the Dutch CONCOR registry [59••]. Furthermore, data from this registry provide insights into the frequency of PAH in relation to various cardiac defects. Among patients with PDA, about 3 % developed PAH, compared with 7–8 % in ASD, 11 % in VSD, 41 % in atrioventricular septal canal defects and nearly 100 % in aortopulmonary window [59••]. The risk of developing Eisenmenger's syndrome also varies depending on the underlying heart defect, ranging from 10–17 % in patients with an ASD (pre-tricuspid shunt), to 50 % of patients with a VSD (post-tricuspid shunt), 90 % of those with unrepaired AVSD and almost all patients with truncus arteriosus [60, 61].

PAH is an important independent risk factor for CHD. Results from a large retrospective, longitudinal cohort study conducted in a Canadian adult CHD population with 23 years of follow-up demonstrated that diagnosis of pulmonary hypertension in adults with CHD is associated with a more than 2-fold higher risk for all-cause mortality [62]. In the Dutch CONCOR national registry for adult CHD, PH was identified as one of the most important risk factors for mortality, with a hazard ratio of 4.4, 4.7 and 4.8 for the cause of death, heart failure, sudden death and vascular reasons, respectively [63]. For patients with Eisenmenger's syndrome, median survival rate is reduced by approximately 20 years compared with healthy individuals. A recent study of 229 patients with Eisenmenger's syndrome, who were treated between 1999 and 2008 in an UK center, revealed that 52 of the 229 patients died during follow-up (median 4 years) and the vast majority of deaths occurred in the patients who did not receive PAH-specific therapy [64••]. However, in a retrospective study published most recently, patients with PAH after cardiac defect correction have a far worse long-term outcomes than any other type of PAH-CHD, such as Eisenmenger's syndrome, PAH associated with systemic-to-pulmonary shunts and PAH associated with small defects [65••].

Human Immunodeficiency Virus (HIV)

HIV infection is an established risk factor for the development of PAH. In comparison with the incidence of IPAH in the general population, HIV-infected patients have a 2,500-fold risk of developing PAH. In the French PAH Registry, PAH-HIV represented around 7 % of all the enrolled cases of PAH [8••], while only 2.0 % of those in US-based REVEAL registry [11•] and 2.3 % of those in Europe-based COMPARE registry [16]. Initial studies in the early 1990s—a time when therapy with highly active antiretroviral therapy (HAART) was not yet available—indicated a PAH prevalence of 0.5 % in HIV-infected patients [66]. In the current HAART era, a prospective study conducted with more than 7,500 HIV infected patients demonstrated a prevalence of 0.46 % [67]. Although the prevalence of PAH-HIV seems to have not changed in recent years, recent data from the Swiss HIV Cohort Study indicate that the incidence declined from 0.21 % in 1995 to only 0.03 % in 2006 [68]. This decrease in incidence may be related to improvements in HAART and corresponding higher CD4 cell counts and lower immune activation [68].

The symptoms, hemodynamic findings, and survival of patients with PAH associated with HIV are similar to those of patients with IPAH. The presence of PAH is an independent risk factor for mortality in patients with HIV infection, and in most cases death is causally related to PAH rather than to other complications of HIV infection [69]. In a recent report, we showed that prognosis in PAH-HIV in the current therapeutic era is mainly related to CD4+ lymphocyte count and cardiac function [70].

Portopulmonary Hypertension (PoPH)

PoPH is an uncommon pulmonary vascular consequence of portal hypertension. There is no relationship between the existence and degree of POPH and the severity of advanced liver disease. PoPH accounts for approximately 3.9–10.4 % of cases of Group 1 PAH [8••, 11•, 16]. The frequency of PAH in patients with liver disease has not been established.

In 1983, a large autopsy study reported that the prevalence of PAH in patients with cirrhosis was 0.73 % compared with 0.13 % in the overall cohort of unselected patients [71]. A prospective hemodynamic study reported that the prevalence of PAH was 2 % in hospitalized patients with portal hypertension [72]. In the French National Center, Le Pavec et al. described 154 patients with PoPH comprising approximately 10 % of all referred PAH cases from 1984 to 2004 [73]. However, the prevalence in liver transplant patients may be higher. The largest PoPH–liver transplant center experiences reported to date documented frequencies of 8.5 % (Baylor Medical Center, Dallas TX, USA: 102 out of 1,205), 6.1 % (Clamart, France: 10 out of 165), and 5.3 % (Mayo Clinic: 66 out of 1,235) of PoPH in patients considered for liver transplantation [74–76].

Little is known regarding the impact of current therapies on survival in PoPH, as patients with PoPH have been excluded from almost all of the major prospective clinical treatment trials. However, even with the use of such therapies, patients with PoPH had significantly poorer survival and all-cause hospitalization rates compared with IPAH/FPAH, despite having better hemodynamics at diagnosis. In US-based REVEAL registry, 174 patients with POPH, survival at 2 and 5 years

was 67 and 40 %, respectively, as compared with 85 and 64 %, respectively, in 1,478 patients with IPAH [77•].

The presence of PAH, however, increases the perioperative mortality, and an mPAP above 50 mm Hg is considered a contraindication to liver transplantation at most centers [78]. Although therapy to lower mPAP has permitted successful orthotopic liver transplantation in some patients, the pulmonary vascular abnormalities of PAH are not consistently reversed by liver transplantation in majority patients.

Drugs or Toxins

Appetite Suppressant Drugs

The identification of drugs and toxins as risk factors for PAH poses a great challenge to both the physician and the epidemiologist: their role in pathogenesis may be suggested from the drug and social history, and the setting up of cohort or case- control studies from large patient databases is important to assess the probability of causality. An epidemic of PAH erupted in Switzerland, Austria, and Germany between 1966 and 1968, when the incidence increased 20-fold following the introduction in those countries of the appetite-depressant aminorex fumarate [79]. The incidence of PAH in patients who had used aminorex was shown to be about 0.2 % overall [80], and related to the amount of drug taken. Furthermore, if discontinued early enough, a regression of PAH could be seen [81]. In a European registry including 95 PAH patients, the odds ratio for developing PAH was 6.3 after any anorectic agent exposure, and the odds ratio sharply increased to 23.8 when patients had taken anorectic agents for longer than 3 months [82•]. Likewise, similar results were also obtained in the North American population. In a multicenter registry, a history of fenfluramine exposure in 579 patients was strongly associated with the development of PAH [83]. Recently, in a French single-center study with over a 10-year follow-up, the interval between the initial exposure to fenfluramine and the onset of dyspnea was approximately 4 years [84]. Large PAH registries initiated in this century have shown that approximately 2–9.5 % of patients had a history of anorexigen exposure [8••, 11•, 16]. Survival implications are probably that there is no difference between patients with fenfluramine-induced PAH and those with idiopathic and heritable PAH [84], although a smaller US study did suggest that survival was worse in patients with fenfluramine-induced PAH compared to those with idiopathic or heritable PAH (median 1.2 vs. 4.1 years) [85].

Dasatinib

Dasatinib, a dual Src/Abl kinase inhibitor, used in the treatment of chronic myelogenous leukaemia was associated with cases of severe PAH [86]. Median delay between initiation of dasatinib and PAH diagnosis was 34 months. At diagnosis, most patients had severe clinical, functional and hemodynamic impairment. Clinical and functional improvements were usually observed after dasatinib discontinuation. Indeed, the majority of patients failed to demonstrate complete hemodynamic recovery and two patients died at follow-up. No predictive factor (including clinical comorbidities or BMPR2 genetic status) of dasatinib related-toxicity was detected in the study. Authors estimated the lowest incidence of PH in patients exposed to dasatinib at 0.45 %. Interestingly, all patients had previously received imatinib before dasatinib and six patients had received nilotinib after dasatinib discontinuation without PAH recurrence [86].

Amphetamines, phentermine and mazindol were less frequently used but are also considered as possible risk factors for PAH. Recently several studies raised the question of whether endothelial dysfunction could be induced by interferons, and a few cases of PAH have been reported with interferon therapy. Other possible risk factors for PAH include: nasal decongestants, such as phenylpropanolamine, dietary supplement–L-Tryptophan, selective serotonin reuptake inhibitors, pergolide and other drugs that could act on 5HT2B receptors. Interestingly, PAH remains a rare complication of these drugs, suggesting possible individual susceptibility, and further studies are needed to identify patients at risk of drug-induced PAH [87].

Schistosomiasis

Schistosomiasis is one of the most prevalent chronic infectious diseases in the world, and is the third leading endemic parasitic disease. The main regions of the world afflicted by it are Sub-Saharan Africa, China, Southeast Asia, and some areas of Latin America, particularly in Brazil. It is believed that about 5 % of patients diagnosed with hepatosplenic schistosomiasis mansoni may also present with PAH (Sch-PAH) [88], suggesting that Sch-PAH is potentially the most prevalent cause of PAH worldwide. Indeed, it is estimated that up to 30 % of all PH patients followed at reference centers in Brazil have Sch-PAH [89].

The clinical features of Sch-PAH are very similar to the ones of IPAH, but less severe and with a longer evolution. The prognosis of Sch-PAH also seems to be better than

IPAH. Recent data demonstrated that independently of hemodynamic severity at baseline, Sch-PAH patients had a better 3-year survival than what would be expected for patients with IPAH, suggesting a more benign course of the disease [90].

Pulmonary Veno-Occlusive Disease (PVOD)

PVOD is a rare form of PH that is characterized by extensive and diffuse obliteration of small pulmonary veins or venules

by cellular proliferation, in situ thrombosis, and fibrous tissue [91]. PVOD and IPAH share a similar clinical presentation, genetic background, and hemodynamic profile. Therefore, PVOD always be misdiagnosed as IPAH and accounts for 5–10 % of cases initially considered as IPAH [92]. As observed in IPAH, PVOD has been diagnosed throughout a very wide age range. With regard to sex distribution, PVOD occurs equally in men and women. The estimated annual incidence of PVOD in the general population has been estimated at 0.1–0.4 cases per million persons per year [92]. However, this may be underestimated because many cases are probably misclassified as IPAH, heart failure, or interstitial lung disease.

The pulmonary vasodilators were far less effective in patients with PVOD compared with other etiologies of PAH, and even had a high risk of severe pulmonary edema. As a result, the survival in PVOD seems to be even more dismal than for IPAH. The most recent series of a group of 24 histologically confirmed severe PVOD patients found a mean time from first symptoms to death of 24.4±22.2 months, which is significantly lower in PVOD when compared to 57.9±38.2 months for patients with IPAH. Therefore, early diagnosis and referral for lung transplantation in appropriate patients are critical in PVOD [93].

The Knowledge Gap of PAH between Developing Countries and Developed Countries

Recent reports from contemporary registries suggested that the WHO group IPAH population, especially typical IPAH patients, are now older and have better survival when compared with patients from the NIH era. As a result of recent developments in PAH management, survival of patients with PAH has markedly improved, as indicated by data from the French, UK and Irish, US REVEAL and European registries. However, despite the significant advances achieved, there is currently little information available on the characteristics of patients with PAH outside North America and Europe.

In 2007, a pioneer registry study in an Asian population was undertaken by Jing et al [94]. Their study reviewed 72 patients with IPAH or familial/heritable PAH from 1999 to 2004; only 20 of these patients underwent right heart catheterization. The study reported similar demographic features, but a poorer prognosis compared with the NIH registry data. Although modern diagnostic strategies and treatment options have been available in China since 2006, the similarities and differences between patients with IPAH in Western countries and China are still unclear.

To define the clinical characteristics of the Chinese patients with WHO Group 1 PAH, and to compare these data with current Western registries, we initiated a new registry and retrospectively collected patients diagnosed as WHO Group 1 PAH from nine pulmonary hypertension centers between May 2008 and May 2011 [50••]. To date, a total of 1,165 patients were diagnosed as Group 1 PAH. Of these, 956 adult patients were included to further analysis and follow-up. Our results demonstrate several striking differences between Chinese and Western PAH patients enrolled in registries in the modern therapy era, such as lower diagnostic age, more patients associated with CHD and SLE, less comorbid conditions. The different distribution of etiologies in PAH between Western registries and new Chinese registries is shown in Fig. 1. However, the preliminary data was collected from patients diagnosed only in referral centers located in big cities. The whole picture of diagnosis, treatment and prognosis in patients with PAH in China, or even in developing countries, still needs to be identified in a larger and nationwide, and/or multinational registry.

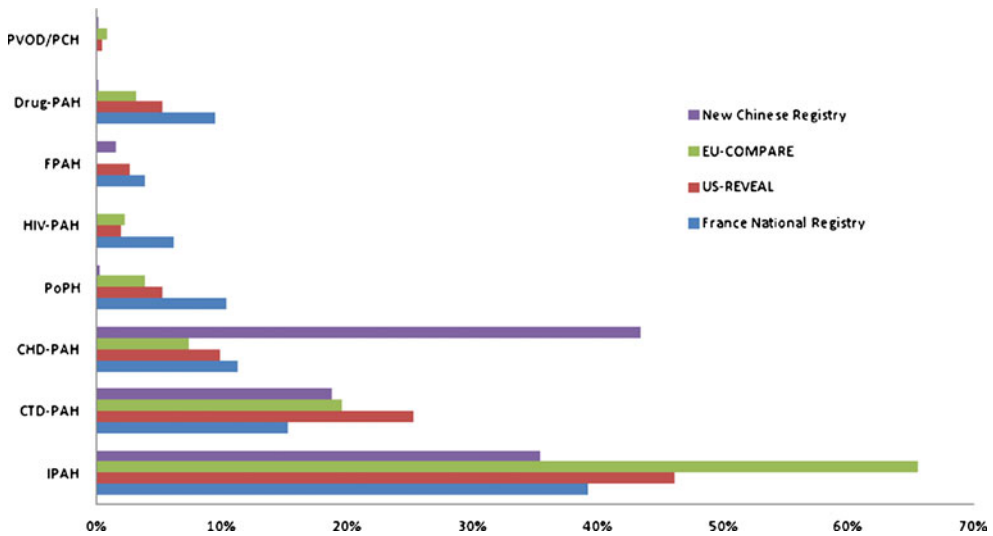

Fig. 1 Etiologies of patients with PAH in the new Chinese registry, US-REVEAL registry, EU-COMPARE registry and French national registry. *CHD-PAH* Congenital heart disease associated with PAH, *CTD-PAH* Connective tissue disease associated with PAH, *Drug-PAH* Drug-induced PAH, *FPAH* Familial PAH, *HIV-PAH* Human immunodeficiency virus infection-related PAH, *PoPH* Portopulmonary hypertension, *PVOD/PCH* Pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis

Conclusion

The epidemiology of PAH is changing in last decade. Remarkable advances in understanding the pathobiology and clinical care in PAH have resulted in improved quality of life and survival. Despite such important progress, however, the long-term survival rate remains unacceptable. The epidemiology of PAH could not be easily generalized globally, due to the fact that nearly all of the present data has been gathered from Western, multicenter, prospective registries. There are potentially marked differences in patients with PAH from Western and Eastern populations, and from developed and developing countries. Therefore, it is clear that more registry data will be needed to address novel questions emerging from an improved understanding of PAH.

Compliance with Ethics Guidelines

Conflict of Interest Xin Jiang and Zhi-Cheng Jing declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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