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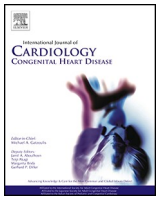

Pulmonary hypertension aetiologies in different parts of the world

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A B S T R A C T

Pulmonary hypertension is a serious condition characterised by elevated blood pressure in the pulmonary arteries, caused by various aetiologies and via different pathological processes. Over the past seventy years, our understanding and management of this disorder have greatly improved, resulting in increased diagnosis and effective clinical management. Current epidemiological estimates are challenged by the increased awareness of this condition and the changing definitions and classification systems. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) has also shown temporal changes in the epidemiology of pulmonary hypertension over the last thirty years, contributing to regional variations in prevalence and incidence.

This review explores the complexities of global and regional variations in different types of pulmonary hypertension reported through many registries, databases and regional studies. Although these tools can help estimate prevalence and incidences, they may also underestimate the actual number of cases due to the continuously changing understanding of the condition and increase awareness globally. Therefore, continued research, international collaboration, and standardised data collection are essential for achieving a more accurate global view of pulmonary hypertension and developing effective management strategies for this serious condition that significantly impacts general health.

1. Introduction

Pulmonary hypertension is a serious condition marked by elevated blood pressure in the pulmonary arteries. This pressure significantly strains the heart, particularly the right ventricle, potentially leading to heart failure and even death. The condition is complex and has various aetiologies that impact the pulmonary vasculature through different pathological processes. Over the past seven decades, the medical community's understanding of pulmonary hypertension has evolved considerably.

In October 1960, the World Health Organization (WHO) convened an expert committee on chronic cor pulmonale in Geneva, Switzerland, establishing vital diagnostic criteria. Initially, pulmonary hypertension was defined as a mean pulmonary artery pressure of ≥25 mm Hg at rest, determined through right heart catheterisation. The condition was broadly divided into two primary categories: Pre-capillary pulmonary hypertension, characterised by a pulmonary artery wedge pressure of ≤15 mm Hg, and Post-capillary pulmonary hypertension, where the wedge pressure exceeds 15 mm Hg [1]. The evolving understanding of pulmonary hypertension has prompted significant revisions to this definition and classification. As of June 2024, during The Seventh World Symposium on Pulmonary Hypertension held in Barcelona, Spain, the new definition has been approved of what was originally suggested in proposed during the 6th World Symposium on Pulmonary Hypertension in 2018 [2] to characterise the condition as a haemodynamic abnormality marked by a mean pulmonary artery pressure exceeding 20 mm Hg, as assessed through right heart catheterisation. The revised classification encompasses [3].

- Pre-capillary: pulmonary artery wedge pressure ≤15 mmHg and pulmonary vascular resistance >2 Wood Units
- Post-capillary: pulmonary artery wedge pressure >15 mm Hg and pulmonary vascular resistance ≤2 Wood Units
- Combined post- and pre-capillary: pulmonary artery wedge pressure >15 mm Hg and pulmonary vascular resistance >2 Wood Units

Furthermore, the evolution of pulmonary hypertension classification has been a dynamic process spanning several decades. The first WHO meeting in 1960 marked a pivotal moment in comprehending pulmonary hypertension pathology. A significant advancement occurred in September 1998 during the World Symposium on Primary Pulmonary Hypertension in Evian, France. This symposium introduced an updated diagnostic classification primarily categorising pulmonary hypertension into five groups based on pathological lesions and adopted it for clinical application. The term "pulmonary arterial hypertension" was incorporated, recognising that it could occur independently or be associated

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with various conditions. The Evian classification has been continuously revised at subsequent World Symposia, mainly: Third World Symposium on Pulmonary Arterial Hypertension in Venice, Italy (June 2003, Fourth World Symposium on Pulmonary Arterial Hypertension in Dana Point, USA (February 2008); Fifth World Symposium on Pulmonary Hypertension in Nice, France (February 2013) and Sixth World Symposium on Pulmonary Hypertension in Nice (February 2018). The Seventh World Symposium on Pulmonary Hypertension, held in June 2024 in Barcelona, Spain, approved a revision in the classification of pulmonary hypertension (Table 1) [4]

The ongoing refinement of pulmonary hypertension classification highlights the intricate nature of this condition and the continuous advancements in medical understanding. As research evolves, further modifications to the classification system are anticipated, particularly regarding biomarkers and genetic predispositions that could facilitate a personalised approach. This shift may influence diagnostic criteria, treatment strategies, and epidemiological insights.

The revised definition and classification present data interpretation and comparison challenges across different periods and world regions. Most existing studies have utilised the older definition, potentially underestimating the true prevalence of pulmonary hypertension. As future studies adopt the revised criteria, pulmonary hypertension's reported prevalence may increase significantly. The medical community must adapt to these new criteria, potentially leading to earlier diagnosis and intervention for patients with pulmonary hypertension. It also highlights the need for careful consideration when comparing historical data with recent findings, as the underlying definitions may differ substantially. It is crucial to recognise that these classifications may continue to evolve as new research emerges and our understanding deepens. While existing studies form the basis of current analyses, future findings may alter perspectives on this condition's prevalence and other aspects.

Table 1
Updated clinical classification of pulmonary hypertension as per the Seventh World Symposium on Pulmonary Hypertension, Barcelona, Spain 2024 [4].

Group 1: Pulmonary Arterial Hypertension
1.1 Idiopathic
1.1.1 Long-term responders to calcium channel blockers
1.2 Heritable
1.3 Associated with drugs and toxins
Note: patients with heritable Pulmonary Arterial Hypertension or Pulmonary Arterial Hypertension associated with drugs and toxins might be long-term responders to calcium channel blockers.
1.4 Associated with:
1.4.1 Connective Tissue Disease
1.4.2 HIV infection
1.4.3 Portal Hypertension
1.4.4 Congenital Heart Disease
1.4.5 Schistosomiasis
1.5 Pulmonary Arterial Hypertension with features of venous/capillary involvement
(Pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis)
1.6 Persistent PH of the newborn
Group 2: PH associated with left heart disease
2.1 Heart failure:
2.1.1 With preserved ejection fraction
2.1.2 With reduced or mildly reduced ejection fraction
2.1.3 Cardiomyopathies with specific aetiologies
(Hypertrophic, Amyloid, Fabry disease and Chagas disease)
2.2 Valvular heart disease:
2.2.1 Aortic valve disease
2.2.2 Mitral valve disease
2.2.3 Mixed valvular disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary pulmonary Hypertension Group
Group 3: PH associated with lung diseases and/or hypoxia
3.1 COPD and/or emphysema
3.2 Interstitial lung disease
3.3 Combined pulmonary fibrosis and emphysema
3.4 Other parenchymal lung diseases
(Parenchymal lung diseases not included in the group)
3.5 Nonparenchymal restrictive diseases:
3.5.1 hypoventilation syndromes
3.5.2 Pneumonectomy
3.6 Hypoxia without lung disease (e.g. high altitude)
3.7 Developmental lung diseases
Group 4: PH associated with pulmonary artery obstructions
4.1 Chronic thromboembolic Pulmonary hypertension
4.2 Other pulmonary artery obstructions
(Other causes of pulmonary artery obstructions include sarcomas (high- or intermediate-grade or angiosarcoma), other malignant tumours (e.g. renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), nonmalignant tumours (e.g. uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses and hydatidosis)
Group 5: PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
(including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders)
5.2 Systemic disorders
(Sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1)
5.3 Metabolic disorders
(Including glycogen storage diseases and Gaucher disease.)
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis
5.7 Complex congenital heart disease

2. The epidemiology of pulmonary hypertension

The complexity and multifactorial nature of pulmonary hypertension make the epidemiology of it a challenge. Determining the incidence and prevalence of pulmonary hypertension is still challenging due to the influence of various diagnostic, demographic, and healthcare factors. Advanced diagnostic tools, such as cardiac catheterisation and echocardiography, have significantly impacted our understanding and diagnosis of pulmonary hypertension and its epidemiology [3,4].

PH epidemiological data are primarily derived from registries, databases, and observational studies. [5,6]. These tools are indispensable for estimating the disease's incidence and prevalence. Since establishing the first National Institutes of Health (NIH) pulmonary hypertension registry in the United States, more than 20 registries have been developed worldwide, encompassing data from over 10,000 patients. [5–7]. However, these registries often reflect regional rather than global trends, as their methodologies, diagnostic criteria, and population representations vary significantly.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) [8,9] has started an essential initiative for quantifying the global health impact of pulmonary hypertension. By examining data across various regions and sociodemographic categories—such as income levels, educational attainment, and fertility rates—the GBD study delivers valuable insights into the prevalence, incidence, mortality, and disability associated with Pulmonary hypertension from 1990 to 2021 [10]. While it has limitations, this comprehensive analysis provides one of the most reliable assessments of the global burden of PH.

Several factors complicate the assessment of pulmonary hypertension epidemiology, mainly the lack of standardisation, which complicates direct comparisons across studies. Furthermore, increased awareness due to advancements in therapies, development of new upcoming drug treatments and marketing has led to more frequent diagnoses of new phenotypes of patients with comorbidities in high-income regions with better healthcare access, However, delayed diagnosis remains a pervasive issue, as many patients live with pulmonary vascular pathology for years before symptoms become apparent. This delay is particularly pronounced in underdeveloped regions where limited or unequal healthcare access leads to significant underreporting. Geographic factors also contribute; for instance, living at high altitudes (above 4000 feet) is strongly associated with an increased risk of pulmonary hypertension. Additionally, pollution, socioeconomic disparities, and variations in substance or illicit drug abuse exacerbate these variations across populations and various regions [11].

Future research must prioritise developing and harmonising universally accepted diagnostic criteria and protocols, improving case detection and reporting in low-income regions, and exploring genetic, environmental, behavioural, and socioeconomic factors influencing pulmonary hypertension susceptibility. Standardising registry methodologies is also required because inconsistent practices hinder reliable comparisons and trend analyses. Large-scale studies across diverse populations, particularly in underrepresented areas like Asia and Africa, are essential for capturing regional variations [12].

3. The global and regional aspects of pulmonary arterial hypertension (group 1)

Pulmonary arterial hypertension encompasses various pathological and clinical conditions (Table 1). Despite its heterogeneous nature, pulmonary arterial hypertension is often referred to as a single entity in clinical practice, primarily because most clinical trials for targeted therapies group these diverse clinical entities and pathological conditions into a single cohort [4,13].

Initial estimates from various registries and databases suggested that the incidence of pulmonary arterial hypertension ranged from 2 to 10 cases per million adults annually. However, recent studies have revealed a more complex picture, with prevalence rates varying from 11 to 60 cases per million adults. For instance, the French registry reported a prevalence of 15 cases per million adults for Pulmonary arterial hypertension. In comparison, data from the Scottish Pulmonary Vascular Unit indicated a higher prevalence of 52 cases per million population [5,6,11,14]. Even in the United States, Fling et al. noticed a significant regional variation among participants at accredited pulmonary vascular disease centers in multiple baseline characteristics and mortality [15].

The 2021 Analysis of the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) provided a more recent global perspective, estimating 192,000 prevalent cases of pulmonary arterial hypertension worldwide. The study reported an age-standardised prevalence rate of 2.28 per 100,000 population and an incidence rate of 0.52 per 100,000. Notably, the age-standardised incidence rate of pulmonary arterial hypertension in 2021 exhibited considerable regional variation, ranging from 0.30 per 100,000 in High-income North America to 0.92 per 100,000 in Eastern Sub-Saharan Africa [10,91]. These substantial regional variations can be attributed to several factors, including methodological differences, high-risk factors such as infectious diseases (HIV, schistosomiasis, and other parasitic infections), genetic variations, and environmental factors like altitude and air quality. Moreover, disparities in healthcare access, diagnostic expertise, and available tools contribute to these variations. With their advanced healthcare systems and sophisticated diagnostic equipment, high-income regions tend to have more accurate diagnoses and lower incidence rates. In contrast, regions like Eastern Sub-Saharan Africa, with limited access to advanced diagnostic tools, may rely more heavily on echocardiography than cardiac catheterisation, potentially leading to misdiagnosis or overestimating pulmonary arterial hypertension cases [11,16, 91].

Most registries in the GBD analysis indicate a predominance of females with pulmonary arterial hypertension (2.75 per 100,000) compared to males (1.78 per 100,000), particularly in younger age groups. However, the gender ratio tends to even out in elderly patients. The prevalence in females in Western Europe had the highest age-standardised prevalence rate (3.56 per 100,000), while South Asia had the lowest (1.71 per 100,000). The mortality rates generally increase with age. The highest prevalence was observed in the 75–79 age group, but there was no difference in mortality rates. In the U.S., racial and ethnic differences were observed in pulmonary arterial hypertension aetiology and baseline characteristics across various regions. Body Mass Index (BMI) was highest among participants from the United States and Canada and lowest among Asian or Sub-Saharan Africa. These disparities are due mainly to variations in access to expert centers and healthcare resources across regions, which may affect the timing of referral and the severity of illness when patients are initially seen at a pulmonary hypertension centre [6,10,11,17,91].

The health-related burden of pulmonary arterial hypertension is substantial, with 642,000 Disability-Adjusted Life Years (DALY) attributed to the condition in 2021. This burden is comparable to diseases such as chronic myeloid leukaemia, multiple sclerosis, and Crohn's disease. The majority of this burden comes from years of life lost (YLLs) rather than years lived with disability (YLDs), highlighting the fatal nature of pulmonary arterial hypertension [91].

While the GBD study on pulmonary arterial hypertension provides the most comprehensive global assessment of pulmonary arterial hypertension burden to date, offering valuable insights for health policy and resource allocation, it has limitations. These include data sparsity in some regions, evolving disease definitions, and potential misclassification of pulmonary arterial hypertension cases.

It is essential to mention here that infectious diseases play a significant role in the development of pulmonary vascular disorders, particularly in developing countries. Schistosomiasis, one of the most prevalent parasitic diseases globally, affects over 200 million people worldwide and is endemic in 74 countries, including regions in Africa, Brazil, the Middle East, and Southeast Asia. The pathological mechanism of schistosomiasis-induced pulmonary hypertension involves an immunological reaction triggered by Schistosoma eggs in the lungs, resulting

in granuloma formation and subsequent remodelling of pulmonary arterioles [18]. Other helminthic infections, such as those caused by *Wuchereria bancrofti*, *Clonorchis sinensis*, and Echinococcus species, have also been associated with pulmonary hypertension. However, their epidemiological profiles concerning pulmonary hypertension are not well-established due to limited case reports [19]. Human immunodeficiency virus (HIV) infection has been shown to increase the risk of developing pulmonary hypertension by up to 2000 times. With an estimated 44 million people living with HIV by the end of 2018, the prevalence of HIV-associated pulmonary hypertension ranges from 0.4 % to 11.5 % globally. This translates to approximately 170,000 to 1 million patients worldwide potentially suffering from pulmonary hypertension secondary to HIV infection [20]. Some bacterial infections, such as *Bordetella pertussis* and *Mycobacterium tuberculosis*, have been associated with pulmonary hypertension. In addition, recent reports suggest a potential link between fungal infections, such as *Paracoccidioides brasiliensis*, and pulmonary vascular disease [21–24].

To sum up, pulmonary arterial hypertension is a complex global health challenge with significant regional variations in prevalence and incidence. Infectious diseases significantly impact the worldwide prevalence of pulmonary vascular disorders, but their full epidemiological impact has yet to be fully understood. While recent studies have provided valuable insights, limitations in data collection and evolving disease definitions highlight the need for continued research on regional aspects to fully understand and address the global impact of pulmonary arterial hypertension.

4. The global and regional aspects of pulmonary hypertension due to left heart diseases (group 2)

Pulmonary hypertension caused by left heart disease, known as Group 2 pulmonary hypertension, is the most common form of pulmonary hypertension. This condition arises when left heart disorders increase pulmonary venous pressure, causing elevated pulmonary pressure. The increasing prevalence of heart failure worldwide, particularly in ageing populations, is primarily responsible for the significant global health burden. In fact, pulmonary hypertension related to left heart disease represents the most common form of pulmonary hypertension, accounting for 65–80 % of cases [25]. Heart failure can lead to a worse prognosis due to the common complication of pulmonary hypertension. The development of pulmonary hypertension in heart failure patients is often associated with right ventricular dysfunction, which could double the mortality risk [26].

Group 2 Pulmonary hypertension is further subdivided into two categories: isolated post-capillary pulmonary hypertension (IpcPH) and combined post- and pre-capillary pulmonary hypertension (CpcPH). These subtypes are distinguished based on hemodynamic parameters, particularly pulmonary vascular resistance. CpcPH is associated with more severe symptoms and worse outcomes compared to IpcPH [26–28].

Pulmonary hypertension occurs in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), with a higher prevalence in the latter. The prevalence of pulmonary hypertension, as assessed by right heart catheterisation, ranges between 33 % and 68 % in heart failure patients. In HFpEF, the prevalence is even higher, ranging from 50 % to 80 %. Post-capillary pulmonary hypertension, either isolated or combined with a pre-capillary component, is a frequent complication in both HFrEF and HFpEF, affecting at least 50 % of these patients. The survival rates have improved for patients with HFrEF, but the same cannot be said for those with HFpEF. It was estimated that the mortality rate for HFpEF patients with pulmonary hypertension was 23.6 % at 1 year and 48.2 % at 5 years [29–31].

As of 2013, heart failure affected an estimated 61.7 million people globally, nearly doubling since 1990. The primary causes include ischemic heart disease, hypertensive heart disease, myocarditis, cardiomyopathies, aortic valve diseases and rheumatic heart disease. Heart failure prevalence shows geographic variations, with preliminary data suggesting higher rates in Asia-Pacific compared to Western countries. In developed nations, heart failure predominantly affects older individuals, with over 80 % of patients being 65 years of age or older. On the other hand, recent studies from sub-Saharan Africa have revealed that patients admitted for heart failure treatment are commonly younger. The incidence of all-cause mortality was 31 per cent patients-years [32–34].

The prevalence and incidence of Group 2 pulmonary hypertension associated with heart failure vary significantly across different parts of the world. According to research in North America, specifically in the United States, Pulmonary hypertension affects roughly 25 %–30 % of heart failure patients, with the prevalence increasing to 60–70 % in advanced cases [25,35]. European research indicates a broader range, with pulmonary hypertension prevalence in heart failure patients spanning from 40 % to 75 %, contingent upon the severity of heart failure and from 36 % to 83 % in patients with heart failure with preserved ejection fraction (HFpEF) [25]. A 2018 nationwide inpatient analysis of U.S. hospitalized patients revealed a 12.8 % prevalence of pulmonary hypertension associated with left heart disease. These patients were typically older, more frequently female, and had higher rates of comorbidities. The subtype-specific prevalence varied, ranging from 11.8 % in heart failure with reduced ejection fraction (HFrEF) to 28.5 % in mitral stenosis. Additionally, the analysis documented that a diagnosis of pulmonary hypertension was associated with increased mortality across most left heart disease subtypes, except for HFrEF. Interestingly, the observed prevalence of PH was lower than reported in prior studies, suggesting potential under-recognition in clinical practice. [36]. Asian countries, such as China, Africa, and Australia, have varying prevalence rates between 20 % and 40 %. According to Japanese studies, pulmonary hypertension was present in 42 % of patients with heart failure with preserved ejection fraction (HFpEF) [37].

The regional disparities are caused by multiple factors similar to those observed in Group 1 above. In addition, population demographics have a significant impact on these variations, as ageing populations in developed countries may contribute to higher rates of heart failure and associated pulmonary hypertension. Different regions have different prevalence rates of comorbidities like hypertension, diabetes, and obesity, which are risk factors for heart failure and pulmonary hypertension. These factors collectively underscore the complexity of accurately assessing the global burden of Group 2 pulmonary hypertension and highlight the need for standardised approaches in future research to better understand and address this significant health issue across diverse populations and healthcare systems.

The prevalence of **Aortic Stenosis** increases with age, affecting 1.3 % of individuals aged 60–69 years and 9.8 % of those aged 80–90 years [38]. Several studies indicate that 50–70 % of patients with severe AS develop pulmonary hypertension - In one large cohort study, 86.3 % of patients with moderate or severe aortic stenosis had some degree of pulmonary hypertension, which is associated with approximately doubled mortality risk [39].

Globally**, Rheumatic Heart Disease** affects an estimated 40.5 million people [40,41], causing substantial cardiovascular morbidity and mortality, especially among younger populations [42]. It remains a significant cause of pulmonary hypertension, particularly in developing countries. The prevalence of pulmonary hypertension in patients with Rheumatic Heart Disease varies widely (10–70 %) depending on the severity of valve disease. [40,41,43]. The high prevalence of pulmonary hypertension in Rheumatic Heart Disease patients underscores the importance of early detection and management to prevent the development of this severe complication [42].

Congenital heart diseases significantly influence the development of pulmonary vascular diseases and could cause pulmonary hypertension. Although some of these are part of pulmonary arterial hypertension, the prevalence of pulmonary hypertension can be significantly

different depending on the type and severity of the cardiac lesion. The CONCOR (CONgenital COR vitia) registry, a Dutch national registry for adult congenital heart disease, provides valuable insights into the prevalence of pulmonary hypertension in congenital heart disease patients with a prevalence of pulmonary hypertension of 4.2 % [44,45]. This figure aligns closely with other studies, which report a 5–10 % prevalence range in adult congenital heart disease populations [46]. The prevalence of congenital heart disease is estimated to be about 1 % of live births [46,47]. This could indeed result in millions of affected individuals worldwide. However, exact figures can vary based on different studies and populations. The outcome of surgical intervention also plays a crucial role in determining the risk of developing pulmonary hypertension. Even after defect correction, about 3 % of patients still develop pulmonary hypertension [48]. This underscores the importance of long-term follow-up for congenital heart disease patients, even after surgical correction.

5. The global and regional aspects of pulmonary hypertension associated with lung diseases and hypoxia (group 3)

This category encompasses a range of respiratory disorders, including chronic obstructive pulmonary disease, interstitial lung diseases and high-altitude pulmonary hypertension (Table 1). These conditions contribute significantly to the global burden of Pulmonary Hypertension, with varying prevalence, pathophysiology, and clinical outcomes across regions.

Chronic Obstructive Pulmonary Disease (COPD) is indeed one of the leading causes of morbidity and mortality worldwide. According to the Global Burden of Disease Study 2019, there were 212.3 million prevalent cases of COPD globally in 2019, accounting for 3.3 million deaths [49]. The statement that approximately 90 % of COPD-related deaths occur in low- and middle-income countries is supported by data from the World Health Organization [50]. There are significant regional Variations with high prevalence in Asia high prevalence [51, 54], whereby in China alone, 45.2 million COPD cases were recorded in 2019, mainly due to air pollution and smoking [52]. Meanwhile, there is evidence of Increasing prevalence in Sub-Saharan Africa, and it is projected to become the region with the highest prevalence (15.1 %) by 2050 [53].

Pulmonary hypertension is a common complication in COPD patients, with prevalence estimates varying widely. Studies have reported prevalence ranges from 20 to 91 % in COPD patients [54,55], with up to 50 % of patients with advanced COPD referred for lung transplantation or lung volume reduction surgery having pulmonary artery pressures over 25 mmHg [56,57]. The mortality impact of pulmonary hypertension in COPD is significant. Studies have shown that COPD patients with pulmonary hypertension have approximately twice the mortality rate compared to those without pulmonary hypertension, even when adjusting for other variables [58]. Based on these figures, the number of individuals affected by pulmonary hypertension secondary to COPD could range from approximately 22.5 to 151.3 million worldwide.

Interstitial Lung Disease (ILD) can cause pulmonary hypertension, a complication that will worsen prognosis and survival outcomes. Among all pathological variants of ILDs, idiopathic pulmonary fibrosis (IPF) is the most extensively studied in relation to pulmonary hypertension. IPF is a chronic, progressive, and fibrotic lung disease that predominantly affects individuals over 60 years of age. Global estimates range from 5.7 to 45.1 per 100,000 in Asia-Pacific countries, 3.3 to 25.1 per 100,000 in Europe, and 14 to 63 per 100,000 in North America [6]. The wide variation in prevalence estimates can be attributed to several factors, including the availability of expert centers in different regions and among studies [59,60]. The global prevalence of IPF is increasing due to improved diagnostic capabilities and ageing populations.

IPF can cause pulmonary hypertension in 14–50 % of IPF patients, but this prevalence increases with IPF severity [61,62]. The progressive fibrosis in IPF destroys the pulmonary capillary bed, reducing the overall vascular surface area and increasing pulmonary vascular resistance. In addition to hypoxia, overexpression of cytokines and growth factors in IPF leads to remodelling of pulmonary blood vessels, contributing to increased vascular resistance [63]. Studies have shown that IPF prevalence increases with age and varies by region. In Europe, IPFpulmonary hypertension prevalence ranged from 1.25 to 23.4 cases per 100,000 population [63], but there is a significant regional variation; for example, in India, a cross-sectional study at a tertiary care centre found that 46 % of ILD patients had echocardiograms suggestive of pulmonary hypertension [64]. The variability in prevalence and presentation across different regions underscores the need for tailored approaches to prevention, early detection, and management strategies for pulmonary hypertension in ILD patients.

High-Altitude Pulmonary Hypertension: Long-term exposure to low oxygen levels at high altitudes causes hypoxic pulmonary vasoconstriction and vascular remodelling, which lead to increased pulmonary vascular resistance and right ventricular hypertrophy [65,66]. This is the primary factor in the development of High-altitude pulmonary hypertension. High-Altitude Pulmonary Hypertension is a significant health concern affecting populations living at high elevations. Approximately 500.3 million humans live at $\geq$1500 m, 81.6 million at $\geq$2500 m, and 14.4 million at $\geq$3500 m [67], which puts many at risk of developing this condition.

The prevalence of High-Altitude Pulmonary Hypertension varies geographically. Studies in the South American Altiplano (above 3200 m) report a 5–18 % prevalence. In China's Qinghai Province, High-Altitude Pulmonary Hypertension is more common in children than adults, with the incidence rising sharply at higher altitudes. Conversely, Tibetan populations show lower High-Altitude Pulmonary Hypertension rates in children and adults, hinting at a potential genetic adaptation to high altitude. However, a separate study of 300 adult Tibetan High-Altitude Pulmonary Hypertension patients revealed severe pulmonary hypertension and right ventricular enlargement, highlighting the disease's severity even in a seemingly well-adapted population [68]. This makes an estimated 7 to 25 million people potentially affected globally.

Genetic factors are the main contributors to the regional variation, with a strong association between the prevalence of pulmonary arterial hypertension and residence at altitudes above 4000 feet (1219 m) [69]. The duration of high-altitude exposure and local environmental factors such as air pollution levels, diet, and lifestyle factors may contribute to regional variations in the prevalence of high-altitude pulmonary hypertension. [70]. Underlying health conditions such as congenital heart defects, such as patent ductus arteriosus, can increase the risk of developing pulmonary hypertension at high altitudes. The prevalence of such conditions may vary between regions [71]. An important observation is that populations with a long history of living at high altitudes have developed unique physiological and genetic adaptations to overcome low oxygen levels [72]. These regional variations underscore the complexity of High-Altitude Pulmonary Hypertension and highlight the need for tailored approaches to prevention, early detection, and management in different high-altitude communities worldwide.

6. The global and regional aspects of pulmonary hypertension associated with pulmonary artery obstructions (group 4)

Chronic thromboembolic pulmonary hypertension (CTEPH) is indeed a rare but severe form of pulmonary hypertension that develops as a long-term complication in a small proportion of patients who experience acute pulmonary embolism [73,74]. It is classified under Group 4 in the current pulmonary hypertension classification system (Table 1). It is characterised by persistent obstruction of the pulmonary arteries due to unresolved thromboembolism and secondary vascular remodelling [75].

The global epidemiology of CTEPH remains incompletely understood, but recent studies have provided some insights. The estimated annual incidence of CTEPH ranges from 3 to 6 cases per million

population in European and USA healthcare systems [30,76]. While the overall incidence of PE is significantly lower than in Western countries, a prospective multicenter observational cohort study was conducted across 17 high-volume centers in Germany to evaluate the outcomes following acute pulmonary embolism. The estimated cumulative incidence of CTEPH over a two-year period was 2.3 %. Patients who developed post-pulmonary embolism impairment (PPEI) experienced a significant increase in incidence (6.0 %), which is defined by persistent or worsening clinical, functional, biochemical, and imaging parameters during follow-up. [77]. Patients with PPEI exhibited an increased risk of rehospitalization and mortality, as well as a markedly reduced quality of life compared to those without PPEI. [77]. in Japan, a higher proportion of CTEPH cases occur without a history of acute pulmonary embolism (15–33 %), compared to approximately 25 % in Western populations. [78]. In other Asian countries such as China, higher incidences than those reported in Europe have been observed in some studies, most likely due to a well-organised pulmonary embolism program in China [79].

Despite advances in awareness, diagnostic techniques, and treatment options, CTEPH remains significantly underdiagnosed worldwide. This underdiagnosis can be attributed to several factors, primarily non-specific symptoms, which are easily mistaken for other conditions. [75]. Additionally, the CTEPH global cross-sectional scientific survey (CLARITY) revealed that there is often a lack of specialised expertise required for accurate diagnosis and interpretation of specific diagnostic procedures. For instance, in South America and the Asia-Pacific regions, expertise is frequently limited in conducting essential diagnostic procedures such as right heart catheterisation or ventilation/perfusion (V/Q) [80].

7. The global and regional aspects of pulmonary hypertension with multifactorial mechanisms (group 5)

This heterogeneous group comprises pulmonary hypertension related to conditions whose mechanisms are unclear or multifactorial (Table 1); both pre-capillary and post-capillary components can be involved. Haematological disorders, principally haemoglobinopathies, constitute a significant subset of this group. The incidence, aetiology, and treatment remain uncertain for many of these conditions. The true prevalence defined by the gold standard of right heart catheterisation is unknown in most of these disorders, and the causal processes are frequently multifactorial. Hemoglobinopathies, which are the leading cause of chronic haemolytic anaemia, are among the most common genetic disorders worldwide. Approximately 5 % of the world's population carries trait genes for haemoglobin disorders, mainly sickle cell disease and thalassemia. It is estimated that over 300,000 babies with severe haemoglobin disorders are born each year [81].

Chronic haemolytic anaemia has been increasingly identified as a risk factor for the development of pulmonary hypertension [82,83]. The pathogenesis of pulmonary hypertension in haemolytic disorders is likely multifactorial, including haemolysis, impaired nitric oxide bioavailability, chronic hypoxemia, chronic thromboembolic disease, chronic liver disease, and asplenia [84]. In addition, chronic anemia in haemolytic disorders triggers compensatory mechanisms to maintain tissue oxygenation, including increased cardiac output. This high-output state strains the pulmonary vasculature, leading to elevated pulmonary artery pressures without a proportional rise in pulmonary vascular resistance (PVR <2 Wood units) in addition to thromboembolic complication [82]. Pulmonary hypertension has emerged as a significant cause of morbidity and mortality in patients with hemoglobinopathies and chronic haemolytic anaemias [83]. At the Fifth World Symposium on pulmonary hypertension in 2013, pulmonary hypertension associated with chronic haemolytic anaemia, including sickle cell disease, was reclassified from Group 1 to Group 5 [84,85]. This reclassification reflected the growing recognition of pulmonary hypertension's complex and multifactorial nature in these conditions.

Based on studies using right heart catheterisation for diagnosis, the prevalence of pulmonary hypertension in sickle cell disease varies from 6 % to 10.4 %. Three studies reported prevalence rates of 6.0 %, 10.0 %, and 10.4 % in adult sickle cell disease populations. [86,87]. The United Nations estimates that 20–25 million people worldwide live with sickle cell disease, with 12–15 million in Africa. In 2021, the number of people living with sickle cell disease globally was estimated at 7.74 million [88]. Pulmonary hypertension in sickle cell disease is associated with high mortality. Studies have reported 2-year mortality rates of approximately 50 % for sickle cell disease patients with pulmonary hypertension. The risk of death for sickle cell disease patients with pulmonary hypertension is 3.4–10.6 times higher compared to those without [89].

For thalassemia, which predominantly occurs in the Mediterranean basin, the global prevalence was reported as 1,310,407 cases, with an incidence of 119,679 new cases that year [88]. The prevalence of pulmonary hypertension in thalassemia ranges from 2.1 % to 6.2 % based on right heart catheterisation studies, but 10–75 % exhibit elevated pulmonary artery pressures on echocardiography [90].

8. Conclusion

Pulmonary hypertension, a significant global and regional health concern, has seen substantial advancements in our understanding and management in recent years. The prevalence of diagnosed and adequately managed cases has significantly increased thanks to enhanced awareness, improved diagnostic techniques, and the development of targeted therapies. However, current epidemiological estimates face limitations due to continuous changes in the definitions and revisions in disease classification systems. Recent data from The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) [8–10,91] have also highlighted the importance of temporal changes in the epidemiology of pulmonary hypertension, contributing to evolving patterns and regional variations in disease prevalence and distribution.

The growing body of evidence and clinical experience has led to a paradigm shift in the perception of pulmonary hypertension. It is no longer considered an orphan disease [17], reflecting the substantial progress in understanding and managing the condition. The evolving landscape of pulmonary hypertension underscores the critical need for continued research, international collaboration, and standardised data collection. These efforts are crucial to obtain a more accurate global picture of pulmonary hypertension, improve our understanding of its global impact, and facilitate cross-regional comparisons to develop more effective management and prevention strategies.

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Declaration of competing interest

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