Pulmonary arterial hypertension in the elderly population

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Abstract: Pulmonary arterial hypertension (PAH) was a disease predominantly affecting young females about 40 years ago; however, it has been increasingly diagnosed in elderly individuals. Few studies have investigated the features of elderly patients with PAH. This review provides an overview of the characteristics of elderly patients with PAH compared to young patients. The examination of the changing demographics of the population with PAH revealed that the mean age has increased over the years. In addition, the investigation into the diagnostic challenges in elderly patients with PAH revealed the difficulty in differentiating PAH from pulmonary hypertension secondary to diastolic heart failure. Moreover, it was noted that elderly patients underwent combination drug regimens less frequently and exhibited poorer treatment responses than young patients. Finally, it was found that elderly PAH patients experienced poorer survival than young patients. The differences among five survival prediction models and their applicability in predicting the prognosis of PAH patients are discussed.

Keywords: Diastolic heart failure; Elderly patients; Pulmonary arterial hypertension

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by pulmonary arterial precapillary remodeling, resulting in increased pulmonary vascular resistance, right heart failure, and, ultimately, death if untreated. PAH is a relatively rare subtype of pulmonary hypertension (PH), which may occur in association with various diseases, including connective tissue disease, congenital heart disease, infections, such as human immunodeficiency virus infection and schistosomiasis, portal vein hypertension, and chronic hemolytic anemia. Although exposure to drugs or toxins and genetic mutations are also causes of PAH, most cases of PAH are idiopathic in origin.[1,2]

PAH is defined by a resting mean pulmonary arterial pressure (mPAP) >20 mmHg and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg.[3] In the 1980s, PAH was believed to primarily affect young women;[4] however, several recent studies have reported a significantly higher mean age of patients with PAH than before.[5–10] Despite the changing demographics of PAH, a limited number of studies have examined the characteristics of elderly individuals diagnosed with PAH. This review aims to provide information regarding the epidemiology, hemodynamic parameters, diagnostic challenges, treatment, and survival of elderly PAH patients.

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2. CHANGING DEMOGRAPHICS OF PAH IN THE ELDERLY POPULATIONS

In the first registry of PAH conducted by the National Institutes of Health between 1981 and 1985, only 9% of patients were >60 years of age with a mean (± SD) age of 36 ± 15 years.[4] However, most current studies have reported an increase in the mean age and proportion of elderly patients among the PAH population.

Among 674 patients with PAH in a National Registry in France analyzing incident and prevalent cases of PAH between October 2002 and October 2003, approximately one-fourth of patients were >60 years of age. Moreover, the mean age of patients with PAH in this registry was 50 ± 15 years.[6]

Results from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), the largest multicenter observational study to date in the United States enrolling 2535 patients with newly and previously diagnosed PAH between March 2006 and September 2007, also confirmed that the mean age of patients with PAH was 53 ± 14 years, with 16.9% >65 years of age.[5]

The Pulmonary Hypertension Registry of the United Kingdom and Ireland, which included 482 purely incident and treatment-naïve patients with PAH diagnosed between January 1, 2001, and December 31, 2009, reported a mean age of 50.1 ± 17.1 years, and 13.5% of patients were >70 years. Furthermore, a comparison of baseline characteristics according to the year of diagnosis (2001-2003 versus 2004-2006 versus 2007-2009) found that patients in the later cohort were older than those in the earlier cohort.[7]

Apart from the studies described above, the Spanish registry (2007-2008),[10] Assessing the Spectrum of Pulmonary Hypertension

Identified at a Referral Center (2001-2010),[9] and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry (2007-2011)[8] all reported an increase in the mean age of patients with PAH compared to that in the National Institutes of Health (NIH) registry (ranging from 45 ± 17 years to 66 ± 9 years). The COMPERA registry even reported that 63% of patients were >65 years (Table 1).

Nevertheless, whether it is the population of PAH itself that is changing, or other factors independent of PAH that cause changes in PAH demographics, remains controversial.[11] Increased awareness among physicians of PAH prevalence in elderly patients, elevated interest in PH by physicians, updated diagnostic algorisms, and/or the increased use of noninvasive screening tools are all possible factors that influence the data of recent registries. Moreover, the difference between healthcare systems and different distributions of population age among countries conducting a registry may lead to divergent epidemiological data. For example, the mean age of PAH patients in a Chinese PAH registry from 1999 to 2004 was 35.9 ± 12.2 years (Table 1), which is quite different from those of other concurrent registries.[12]

In summary, most registries in Western countries in the past 20 years have reported an increasing trend in the mean age of patients with PAH. However, this trend could be the result of several factors independent of the disease itself. Registries in different countries have also reported different epidemiological profiles. However, most recent registry data continue to suggest that the average age of PAH patients is increasing, and this is an important factor in the approach and management of patients with PAH.

3. DIAGNOSTIC CHALLENGES IN ELDERLY PATIENTS WITH PAH

Differentiating PAH from PH with heart failure is one of the most significant diagnostic challenges in elderly patients with PH. PH in association with heart failure with preserved ejection fraction (HFpEF) is increasingly recognized as a cause of PH in elderly patients because increased left ventricular (LV) diastolic pressure is common among this population. PH associated with heart failure is categorized as group 2 PH, and it is often termed "post-capillary PH". On the contrary, PAH is categorized as group 1 PH and is often termed "pre-capillary PH". Although these two types of PH both require the mPAP to exceed 20 mmHg, their pathophysiology is quite different. In the former case, PH is a result of elevated hydrostatic pressure in the left atrium, which is passively transmitted back to the pulmonary circulation. In the latter case, PH is caused by true pulmonary vasculopathy.[13] To differentiate pre- from post-capillary PH, the PCWP must be <15 mmHg.

However, the current definition of PAH (that is, an mPAP >20 mmHg and PCWP <15 mmHg) cannot always precisely distinguish pre- and post-capillary PH. Shapiro et al.[14] examined 48 patients >65 years of age with a presumptive diagnosis of idiopathic PAH (IPAH) and found that 56% exhibited a PCWP >15 mmHg, thereby not fulfilling hemodynamic criterion for IPAH. Before the evaluation of the PCWP, all patients had undergone an extensive evaluation to exclude PH resulting from other recognized causes. Patients with an ejection fraction (EF) <50%, significant mitral or aortic valve disease, or congenital heart disease were also excluded. Specifically, elderlyindividuals with suspected IPAH and a PCWP >15 mmHg may actually have PH secondary to HFpEF. However, Shapiro et al. proposed that PH with an elevated PCWP may still be PAH and categorized as group 1 PH despite not fulfilling the corresponding hemodynamic criteria. They suggested that, although the PCWP increases with increased LV end-diastolic pressure (LVEDP), elevated LVEDP could actually be a result of chronic right ventricle (RV) overload caused by IPAH, but not a result of HFpEF. According to Little et al.[15] and Sunagawa et al.[16] the impact of the RV on LVEDP is modulated by the relative stiffness of the interventricular septum and the LV free wall. In normal hearts, the interventricular septum is less stiff than LV free wall. Thus, the influence of the RV on LVEDP is apparent. In contrast, the septum is stiffer than the LV free wall in most cases of IPAH because of isolated chronic RV pressure overload. Thus, the impact of the RV on LVEDP is less potent than that in normal hearts, and most patients with IPAH exhibit a normal PCWP. However, vascular, LV systolic, and LV diastolic stiffness in elderly patients increases with age. Shapiro et al. presumed that the increase in LV diastolic stiffness preferentially affects the LV free wall because "the septum is relatively unloaded by the pulmonary circulation". Given the already elevated stiffness of the interventricular septum caused by PH, there is a small difference between septal stiffness and LV free wall stiffness. Therefore, there is enhanced interventricular interdependence. As such, elderly patients could have isolated pulmonary arteriopathy with a PCWP >15 mmHg (Table 2).

Furthermore, Shapiro et al. also reported that patients with PH secondary to severe HFpEF may have a near-normal PCWP due to RV failure. These patients may require exercise testing, in which the PCWP increases after exercise more in patients with PH secondary to severe HFpEF than in those with IPAH. However, some studies have revealed that the PCWP may increase with exercise, possibly due to increased ventricular interdependence with exercise. Therefore, whether exercise testing could be used to distinguish PAH from PH secondary to HFpEF remain unclear. In short, differentiation between classic

Table 1

Mean age and proportion of elderly patients in large registries for pulmonary arterial hypertension

Registry	Study cohort	Study design and time period	Incident or prevalent cases	No. of patients	Mean age (± SD)	Proportion of elderly patients
U.S. NIH[4]	PPH	Prospective, 1981-1985	Incident	187	36 ± 15	9% > 60 yrs
Spanish[10]	Group 1 PH age ≥14 yrs	Retrospective, 1998-2006; prospective, 2007-2008	Incident and Prevalent	866	45 ± 17	NA
French[6]	Group 1 PH, age >18 yrs	Prospective, 2002-2003	Incident and Prevalent	674	50 ± 15	~25% > 60 yrs
UK and Ireland[7]	IPAH, HPAH, and anorexigen associated PAH	Prospective, 2001-2009	Incident	482	50.1 ± 17.1	13.5% > 70 yrs
U.S. REVEAL[5]	Group 1 PH	Prospective, 2006-2007	Incident and Prevalent	2525	50.1 ± 14.4	16.9% > 65 yrs
UK ASPIRE[9]	Group 1 PH	Prospective, 2001-2010	Incident	598	54 ± 18	NA
EU COMPERA[8]	IPAH, age >18 yrs	Prospective, 2007-2011	Incident	587	65 (SD NA), median 71	63% > 65 yrs
Chinese[12]	Idiopathic PAH and familial PAH	Prospective 1999-2004	Incident	72	35.9 ± 12.2	4.2% > 60 yrs

HPAH=heritable pulmonary arterial hypertension; IPAH=idiopathic pulmonary arterial hypertension; NA=not available; NIH=National Institutes of Health; PH=pulmonary hypertension; PPH=primary pulmonary hypertension; REVEAL=Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; UK=United Kingdom; US=United States.

Table 2

Impact of relationship between interventricular septum stiffness and Left ventricular free wall stiffness on pulmonary capillary wedge pressure in pulmonary arterial hypertension (PAH) patients and elderly PAH PPatients[14]

	Normal people	PAH	Elderly patients with PAH
mPAP (mmHg)		>20	>20
PCWP (mmHg)		<15	>15
Interventricular septum stiffness (IVSS)	no significant change	increased [a]	increased [a]
Left ventricular free wall stiffness (LVFWS)	no significant change	no significant change	increased [b]
Relationship between IVSS and LVFWS	IVSS ~= LVFWS	IVSS > LVFWS	IVSS ~= LVFWS
Interventricular interdependence	no significant change	Decreased	no significant change

[a],interventricular septum stiffness increased due to isolated right ventricle pressure overload resulting from pulmonary hypertension.

[b]left ventricular free wall stiffness increased due to increased LV diastolic stiffness resulting from old age.

mPAP=mean pulmonary arterial pressure; PAH=pulmonary arterial hypertension; PCWP=pulmonary capillary wedge pressure; IVSS=interventricular septum stiffness; ~= approximately equal to.

PAH, PAH with elevated PCWP, and PH secondary to HFpEF remains a significant challenge for clinicians.

Another problem with the current definition of PAH is that dehydration and/or reduced intravascular volume may reduce the PCWP, resulting in an erroneous diagnosis of PAH. According to Robbins et al.[17] right heart catheterization (RHC) with volume challenge may help distinguish PH due to LV dysfunction (PH-LVD) from PAH.[17] The authors compared hemodynamic data from patients with confirmed or suspected PH before and after the infusion of 0.5 L normal saline over a period of 5 to 10 min. Baseline hemodynamic examination revealed 207 patients with PAH. Surprisingly, 46 (22.2%) patients exhibited a PCWP >15 mmHg after fluid challenge and were reclassified as occult pulmonary venous hypertension, another term for post-capillary PH. Robbins et al. suggested that fluid challenge before RHC should be included in the diagnostic workup for PH. Nevertheless, there is no consensus as whether to include the fluid challenge in the diagnostic workup. As a result, estimating the proportion of patients with PH-LVD misdiagnosed as PAH is difficult.

Consider the COMPERA registry as an example. In this registry,[8] IPAH was the most common cause of PH among elderly patients. However, most of the participating centers in the COMPERA study did not routinely perform volume challenges during RHC. Therefore, some patients with LV diastolic dysfunction may be misclassified as IPAH.

In contrast, Pugh et al.[18] performed provocative measures, such as fluid challenge or nitroprusside administration, during RHC to diagnose LV diastolic dysfunction. They found that PH due to left heart disease was the most frequent diagnosis (28%) among 246 patients with PH >65 years of age, while PAH comprised only a relatively small proportion of patients in the study (15%).

For these reasons, it is difficult to differentiate post-PH from pre-capillary PH.[19] It is important for clinicians to find a precise method to distinguish the former from the latter, because administering medication specific for pre-capillary PH, such as pulmonary-specific vasodilator, in patients with PH-LVD may worsen their functional status and left heart filling pressures.[20]

4. HEMODYNAMIC PROFILES IN ELDERLY PATIENTS WITH PAH

Several studies have suggested that there is an inverse relationship between the age and mPAP at diagnosis (Table 3). In a single-center, retrospective study, Shimony et al.[21] reported that 47 patients >65 years of age had a lower mPAP than 107 young patients (45.0 ± 11.1 vs. 49.2 ± 11.8 mmHg, respectively; $p = 0.04$). Moreover, they found that the myocardial performance index of the RV (RV-MPI) was lower in elderly patients than in young patients, indicating a better RV adaptation of the elderly to high pulmonary pressure (RV-MPI, 0.48 ± 0.20 vs. 0.62 ± 0.23; $p = 0.006$). Nonetheless, the authors observed reduced survival in elderly patients despite their better hemodynamic profile. Shapiro et al.[14] described this as an unexplained paradox.

The COMPERA registry revealed that the mPAP and pulmonary vascular resistance (PVR) values were much lower in elderly patients than in young patients ($p < 0.001$), and the cardiac index (CI) was similar in both groups ($p = 0.873$).[8] However, exercise capacity and survival were poorer in the elderly group than in the young group. Identical CI in both groups and lower PVR in the elderly group suggested that the RV of young patients were stronger and were able to preserve cardiac output at a higher PVR than elderly patients. In other words, the RV of elderly patients with PH was weaker and was less capable of generating high pulmonary pressure than that of young patients. Consequently, elderly patients tended to become symptomatic at lower PVR levels than young patients.

A smaller cohort study in Japan[22] also reported better hemodynamic data and poorer exercise capacity in the elderly group than in the young group. Furthermore, this Japanese registry revealed that the percent diffusing capacity for carbon monoxide (DLCo) of elderly patients was significantly lower than that of young patients. A registry in the UK and Ireland also noted a lower percentage of DLCo in elderly patients than in young patients. Takahashi et al.[22] suggested that impaired gas exchange may play a role in poor exercise capacity in older patients with PH.

Table 3

Inverse relationship between age and mean pulmonary arterial pressure of pulmonary arterial hypertension patients at diagnosis

Study		Younger group	Older group	*p*
Shimony, et al.[21]	Group information	<65 yrs, n = 107	>65 yrs, n = 47	
	mPAP (mmHg)	49.2 ± 11.8	45.0 ± 11.1	0.04
	Cardiac index (L/min m^2)	2.4 ± 0.8	2.4 ± 0.8	0.98
	RV-MPI	0.62 ± 0.23	0.48 ± 0.20	0.006
COMPERA[8]	Group information	18–65 yrs, n = 209	>65 yrs, n = 378	
	mPAP (mmHg)	50 ± 13	41 ± 10	<0.001
	PVR (Wood units)	12.0 ± 6.3	8.3 ± 4.5	<0.001
	Cardiac index (L/min/m^2)	2.2 ± 0.7	2.2 ± 0.7	0.873
	6MWD (m)	340 ± 131	266 ± 114	<0.001
Japan[22]	Group information	<65 yrs, n = 125	>65 yrs, n = 109	
	mPAP (mmHg)	50.7 ± 17.7	39.2 ± 11.4	<0.0001
	PVR (dyne/s/cm^{-5})	980.7 ± 617.3	675.7 ± 362.4	<0.0001
	Cardiac index (L/min/m^2)	2.6 ± 0.9	2.5 ± 0.7	0.6365
	6MWD (m)	325.0 ± 144.3	224.5 ± 117.3	<0.0001

mPAP=mean pulmonary arterial pressure; PAH=pulmonary arterial hypertension; PVR=pulmonary vascular resistance; RV-MPI=right ventricle- myocardial performance index; yrs=years; 6MWD=6-minute walking distance.

Another possible explanation for the paradox between good hemodynamic profile and poor exercise capacity in elderly patients with PH is that their RV adaptability is worse than that of young patients. In addition, age itself and comorbid diseases among elderly patients may also lead to poor exercise capacity and functional class.

5. TREATMENTS AND TREATMENT RESPONSE

Advances in pharmacological therapies have greatly improved the morbidity and mortality of patients with PAH.[23] However, elderly patients with PAH may benefit less from the rapidly growing number of new agents for PAH than young patients because they underwent combination drug regimen less frequently than young patients.[24] Evidence also demonstrated that elderly patients exhibited a poorer response to these medications than young patients.[8]

A PAH registry from the UK and Ireland reported that a higher proportion of young patients received sequential combination therapy (57.6% vs. 34.5%, respectively; $p < 0.001$), triple therapy (10.6% vs. 1.3%; $p < 0.001$), prostaglandins (51.8% vs. 28.1%; $p < 0.001$), calcium channel blocker (10.2% vs. 3%; $p < 0.002$), and transplantation (5.3% vs. 0.4%; $p < 0.002$) than their elderly counterparts.[7]

The COMPERA registry found that elderly patients were less frequently administered combination therapy with at least two PAH drugs than young patients. Combination therapy was used in 19.2% of young patients compared to 12.7% of elderly patients within 3 months after diagnosis ($p = 0.07$).[8] The gap in the combination therapy rate grew wide 1 year after diagnosis (55.6% vs. 31.6%, respectively; $p < 0.001$); however, this gap diminished thereafter. Moreover, prostacyclin analogs and endothelin receptor antagonists were used less frequently in elderly patients than in young patients (6.3% vs. 14.4%, respectively; $p = 0.003$; 63.2% vs. 71.3%; $p = 0.056$).[8] A Swedish study confirmed that patients <65 years of age were more often treated with dual combination therapy than the elderly patients (46% vs. 23%, respectively). In addition, 6% of patients <45 years of age received triple combination therapy, while no patients in the elderly groups received such therapy (Fig. 1).[25]

In the COMPERA registry, Hoeper et al.[8] noted that elderly patients exhibited a poorer treatment response than young patients. Elderly patients demonstrated less improvement in 6 min walk test results compared to young patients 3 and 12

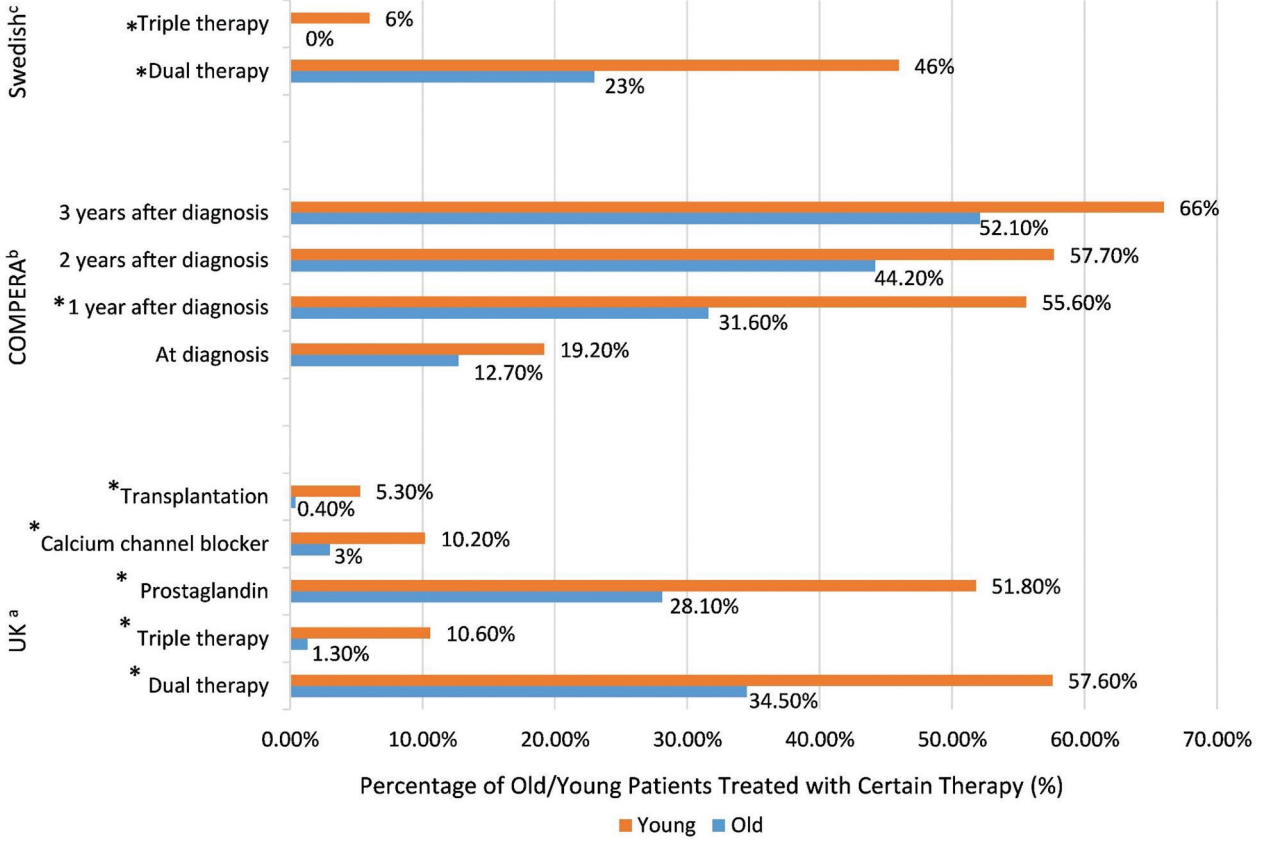

Fig. 1 Difference in the percentage of patients undergoing combination therapy or other specific therapies targeting pulmonary arterial hypertension (PAH) between elderly and young patients with PAH. As shown in the figure, more young PAH patients underwent combination therapy or other specific therapies targeting PAH such as calcium channel blocker, prostaglandin, and organ transplantation, than elderly PAH patients. Although some of the differences in the percentage of patients undergoing these therapies between the young and elderly groups were not statistically significant, the percentage of patients undergoing combination therapies or other specific therapies in the young group was higher than that in the elderly group. Asterisk (*) indicates a statistically significant-difference (that is, $p < 0.05$) in the percentage of patients undergoing combination therapy or other specific therapies targeting PAH between elderly and young patients with PAH. a, Data reproduced from Ling Y, et al. Changing demographics, epidemiology, and survival of incident pulmonary arterial hypertension: results from the pulmonary hypertension registry of the United Kingdom and Ireland. *Am J Respir Crit Care Med* 2012; 186: 790-6. b, The bars in this group indicate the percentage of patients receiving combination therapy at a specific time (at diagnosis, and at 1, 2, and 3 years after diagnosis). Data reproduced from Hoeper et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol* 2013; 168: 871-80. c, Data reproduced from Hjalmarsson C, et al. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2018; 51.

months after therapy (26 m and 30 m vs. 34 m and 50 m, respectively; $p = 0.266$ and $p = 0.028$). Furthermore, the proportion of patients 6-min walk distance >400 m was lower in elderly patients than in young patients. Moreover, fewer elderly patients were found to present with functional class I/II after 1 year of therapy compared to young patients (23% vs. 40%, respectively; $p = 0.002$).

6. SURVIVAL AND PREDICTION EQUATIONS

Few studies have compared the survival of elderly patients with PAH to that of younger patients, although they all reported poorer survival in elderly patients than in young patients. Data from the Pulmonary Hypertension Registry of the UK and Ireland[7] showed that patients ≤50 years of age demonstrated better 1-, 2-, 3-, and 5-year survival rates than their elderly counterpart (94.7%, 91%, 87.2%, and 74.7% vs. 90%, 75.5%, 57.1%, and 43.7%, respectively; $p < 0.001$ [log-rank test]). Furthermore, the COMPERA registry reported that the survival rates of elderly patients (age >65 years) were worse than those of young patients (18-65 years), even when adjusted for the expected survival rates of an age/sex-matched population.

Hjalmarsson et al.[25] reported that patients 18-45 years of age had the highest transplant-free five-year survival rate (88%), while the survival rates were 63%, 56%, and 36% for patients in the age groups 46-64, 65-74 and ≥ 75 years, respectively ($p < 0.001$).

Yi Ling et al.[7] compared the applicability of five survival prediction equations to predict the prognosis of patients with PAH. They predicted the survival of patients enrolled in the UK and Ireland cohorts using these five prediction models, and compared the results to the observed survival of the same patients. These survival prediction equations included the NIH equation,[26] French equation,[27] Pulmonary Hypertension Connection Registry (PHC) equation,[28] REVEAL equation,[29] and REVEAL risk score.[30]

They found that the accuracy of all models declined with time from diagnosis. This could result from a variable disease course influenced by the deterioration of the disease or changes in treatment. The predicted survival from the REVEAL and PHC equations were closest to the observed survival in the UK and Ireland cohort. The French equation slightly underestimated the survival of the same group of patients, and the NIH equation more underrated the survival of PH patients in the same cohort. The NIH equation largely underestimated the outcome of PH patients because it was derived from a cohort before the development of disease-specific therapies. The French equation mildly underrated the outcome of PH patients probably because it was based on a cohort between 2002 and 2006 when currently approved PAH therapies were not available. Another possible explanation is that the French cohort, from which the French equation is derived, excluded mildly ill patients from one of the French University Hospital, whereas the UK and Ireland registry included all patients with PAH of all severities.

In conclusion, over the years, the proportion of elderly patients among the PAH population has increased. An inverse relationship was found between the mPAP and age in patients with PAH. Moreover, it is difficult to differentiate between pre- and post-capillary PH in the elderly population. In addition, less use of combination drug regimens, worse treatment response, and poorer survival rate and exercise capacity were all important issues among elderly PAH patients. To conclude, data regarding the characteristics of elderly patients with PAH remain limited, and further research dedicated to this topic is warranted.

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