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Editorial Comment
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The Changing Landscape of Pulmonary Arterial Hypertension in 21st Century

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Pulmonary hypertension (PH) is a severe, progressive disease characterized by an elevated mean pulmonary artery pressure (mPAP) ≥ 25 mmHg.[1,2] Five PH subgroups have been recognized, but majority of studies on survival have focused on group 1 pulmonary arterial hypertension (PAH) determined by right heart catheterization (RHC) with a mPAP ≥ 25 mmHg, pulmonary arterial wedge pressure (PAWP) < 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units.[3] PAH is characterized by severe remodeling of the distal pulmonary arteries, increased PVR, right ventricular (RV) dysfunction and ultimately heart failure and death.[4]

Over the past 2 decades, the clinical profile of PAH has changed substantially due to the advances in early diagnosis and aggressive pharmacotherapy.[5] PAH has evolved from high mortality and low survival condition (averaged survival time 2.8 years to chronic manageable disease with longer survival time up to 7 years.[6] Indeed, recent PAH studies from patients receiving combination therapy showed that the 3-year survival rate in PAH may be as high as 84% compared with 48% from the original National Institutes of Health (NIH) registry on primary PAH (1980-1985).[7-9]

Collection of patient information into PAH registry databases are important to recognize characterization of demographics, clinical presentations, treatment strategies, outcome of patients and to provide a basis for predicting the course of the disease.[10-14] The Fifth World Symposium for Pulmonary Hypertension (5th WCPH) summarize PAH registries, to outline appropriate interpretation of registry data, and to recommend how registries ought to be pursued for optimal acquisition of useful knowledge in the future.[15] Updated registries show that patients are older at diagnosis (1/4 older than 60 years) than previously reported; disease severity appears greater in men compared with women; and patients with PAH in association with connective tissue disease (CTD) are identified as a particularly high-risk subgroup with worse outcomes. Risk stratification scales for PAH are also available at point of care.[16]

Currently, 11 therapies of targeting 3 PAH-specific pathways (endothelin, nitric oxide and prostacycline) are approved by U.S. Food and Drug Administration (FDA) for clinical use. Since the first oral Endothelin receptor antagonist (ERA) Bosentan was introduced in Taiwan on 2007, 9/11 of above-mentioned therapies (except Tadalafil and oral treprostinil) have been approved in treating PH patients according to the regulation of Taiwan National Health Insurance of Bureau. The indications of PH specific medication are 1. sequential combination of ERA/phosphodiesterase 5 inhibitor (PDE5i) or soluble Guanylate cyclase stimulator (sGCs)/Prostanoids for idiopathic PAH; 2. sequential combination of PDE5i and/or ERA (Bosentan only) for Congenital heart disease (CHD)-PAH, monotherapy of PDE5i for CTD-PAH; and sGCs for inoperable group 4. Chronic ThromboEmbolic PH (CTEPH) patients.

In this issue of Journal, Wang et al. reported a retrospective long-term survival of PAH patient cohort at a

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single center in Northern Taiwan.[17] They collected 70 patients of group 1 PAH since 2002 to 2015. The baseline characteristics included female was predominant (81%) with mean age 41 years, majority (47%) were CTD-PAH; 26% were CHD-PAH; and 14 (20%) were iPAH. During a mean follow up duration of 4.6 years, the overall 1, 3, 5 year survivals were 93%, 88% and 77% respectively. Thirty eight of 70 patients underwent RHC, the rest were diagnosed by echocardiographic study.

Comparing with Western and other Asian population registries (Table 1), they were younger at diagnosis, less patients received PAH specific medication, however the survival rates is comparable. The mean age of patients with PAH in the REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; United States, 2006-2007) and COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; Europe, 2007-2013) registries were 54 and 68 years, respectively, compared with 36 years in the original US NIH iPAH cohort (1980-1985), 38 years in the New Chinese registry (2011) and 41 years in the Wang's report (2017).[7,8,11,13,17,18] The large variability in the mean age of patients with PAH in contemporary registries also may be explained by participation bias among centers, variable accuracy in the diagnostic process and sample size.

The major cause of death of original US NIH iPAH cohort reported in 1991, 73% were due to RHF or sudden death (SD). However, after significant advances in the diagnosis and treatment of this condition got much improvement in 21st century. The Cleveland Clinic reported that a study of 84 patients with PAH (age 58.6 ± 14 yrs, 73% female) who died between June 2008 to May 2012, RHF and SD was the sole cause of death in only 44%.[19] Our unpublished data also shows similar result of iPAH mortality. However, 90% of iPAH and 80% of CTD-PAH patients in Chinese study died of RHF or SD. The differences in phenotype and outcomes might be

Table 1. Demographic, clinical, and hemodynamic characteristics of PAH registries from different countries and time periods

	NIH-PPH[7,8] (1981-85)	French[14,16] (2002-03)	REVEAL[11-21] (2006-09)	UK and Ireland[12] (2001-09)	Gi-PH-Reg[10] (1993-2011)	CHINA[13] (2007-11)	JAPHR[27] (2013-17)	TPHR# (2013-16)	VGHTC# (2006-17)
PAH population, n	194 (PPH)	674 (PAH)	2,716 (PAH)	482 (PAH)	685 (PAH)	173 (PAH)	189 (PAH)	134 (IPAH)	74 (IPAH)
Female gender, %	63	65	79	70	65	70	76	75	81
Mean age, years	36 ± 15	50	50	50	51	33.4 ± 15.3	43.9 ± 16.9	45.82 ± 15.88	48.56 ± 15.92
WHO FC III/IV, %	75	75	56	85	81	66	64	45.73	60.81
mRAP, mmHg	-	8	9	10	8	12.3 ± 6.4	6.6 ± 4.1	14.04 ± 12.11	11.2 ± 6.76
mPAP, mmHg	-	55	50	54	51	63.1 ± 18.0	48.2 ± 13.8	53.18 ± 15.61	51.18 ± 16.71
mPAWP, mmHg	-	8	10	9	8	12.9 ± 4.7	8.2 ± 3.4	10.48 ± 3.17	11.30 ± 2.85
PVR, WU	-	-	11	13	10.58	17.1 ± 9.9	12.95 ± 0.82	15.79 ± 10.04	16.00 ± 10.46
CI, L/min/m^2	-	2.5	2.6	2.1	2.3	2.5 ± 0.9	2.4 ± 0.8	2.21 ± 0.82	1.99 ± 0.81
Treatment, %	0	-	40	99	89	80	100	81	100
Monotherapy	-	-	-	97	72	80.00	75.60	42.53	30.77
Dual combination	-	-	40	2	15	-	22.30	29.85	44.23
Triple combination	-	-			2	-	2.10	8.95	25.00
No PAH therapy	100	-	-	1	11	?(20)	0	18.66	-
Survival									
At 1 year	68	87/83	85/91	78/93	88	92.1/85.4*	97.6	94.44	91.89
At 3 year	48	67/58	68/74	57/73	72	75.1/53.6*	88.2	-	83.78
At 5 year	34	-	57/65	-/61	59	-	-	-	75.68

CI, cardiac index; Gi-PH-Reg, Giessen Pulmonary Hypertension Registry; IPAH, idiopathic pulmonary arterial hypertension; JAPHR, JApan Pulmonary Hypertension Registry; mPAWP, mean pulmonary arterial wedge pressure; mRAP, mean right atrial pressure; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PPH, primary pulmonary hypertension; PVR, pulmonary vascular resistance; REVEAL, Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; TPHR, Taiwan Pulmonary Hypertension Registry (unpublished data); VGHTC, Taichung Veterans General Hospital (unpublished data); WHO, World Health Organization.

* New Chinese PAH registry, IPAH/CTD-PAH; # Unpublished data.

related to the health care environment and lack of aggressive PAH specific therapy rather than to different expressions of the disease.[13,20]

The prevalence of PAH favors women to men by approximately 3.1-fold; however, the clinical profile, hemodynamics at diagnosis, and prognosis in men has appeared to be comparatively less favorable. Multivariate predictors of survival have been described and summarized in Table 2.[20-26]

CONCLUSIONS

Optimizing clinical outcome is closely related to clinical index of suspicion for PAH at the point of care, understanding the broad clinical spectrum of risk, and recognition of the importance of early aggressive therapy in patients with newly diagnosed PAH. Compared with the original clinical experience, PAH has evolved into a contemporary and treatable disease associated with improved survival and decreased morbidity. However, under awareness, and less aggressive treatment among clinicians regarding the importance of early and accurate PAH diagnosis persists and is a potentially reversible cause of adverse outcome in this disease. Health care environment is also an important influencing factor in clinical outcome result.

Table 2. Multivariate predictors of survival in patients of PH[3,20]

Category	Increase risk	Decrease risk
Demographics	Male gender	
	Age (> 65 years old)	
	Etiology: CTD, POPH, HPAH, PVOD	
Functional capacity	Higher NYHA/WHO class (III/VI)	Lower NYHA/WHO class (I/II)
	Lower 6MWD (< 165 meters)	Higher 6MWD (> 440 meters)
Laboratory and biomarkers	Higher BNP (< 50 ng/l) or NT-proBNP (< 300/ng/l)	Lower BNP (> 300 ng/l) or NT-proBNP (> 1400 ng/l)
	Higher creatinine	
Imaging	Echo: pericardial effusion (Presence)	Pericardial effusion (Absence)
	Greater RA chamber size (> 26 cm^2)	Smaller RA chamber size (< 18 cm^2)
Lung function studies	Lower predicted DLCO	Higher predicted DLCO
Hemodynamics	Higher mRAP (> 14 mmHg)	Lower mRAP (< 8 mmHg)
	Lower CO or CI (< 2.0 l/min/m^2)	Higher CO or CI (≥ 2.5l/min/m^2)
	SVO2 < 60%	SVO2 > 65%
	Higher PVR or PVRI	

BNP/NT-proBNP, b-type natriuretic peptide; CI, cardiac index; CO, cardiac output; CTD, connective tissue disease; DLCO, diffusion lung capacity for carbon monoxide; HPAH, heritable pulmonary arterial hypertension; mRAP, mean right atrial pressure; NYHA, New York Heart Association; POPH, portopulmonary hypertension; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SVO2, mixed venous oxygen saturation; WHO, World Health Organization; 6MWD, 6-minute walking distance.

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