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Pulmonary hypertension registry of Kerala, India (PRO-KERALA) — Clinical characteristics and practice patterns

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ABSTRACT

Background: Epidemiological data on pulmonary hypertension (PH) are scarce from developing countries including India.

Methods: We established a multi-center registry of PH, the PRO-KERALA registry, in Kerala, India. Fifty hospitals enrolled consecutive adult (>18 years) patients for one year. Echocardiographic criteria (right ventricular systolic pressure – RVSP > 50 mmHg) or invasively obtained mean pulmonary artery pressure > 25 mmHg was the criteria for entry.

Results: There were 2003 patients (52% Women, mean age 56 ± 16.1 years) enrolled. The mean RVSP was 68.2 (SD = 17.9) mmHg. Majority of the study participants (59%) belonged to group 2 of the WHO Nice Classification 2013 (PH secondary to left heart disease). One-fifth (21.2%) belonged to group 1, while 13.3%, 3.8% and 2.4% of the study population belonged to groups 3, 4 and 5 respectively.

More than a quarter (27%) reported PH due to left heart disease with valvular disease etiology; while 20.7% had coronary artery disease. The other common etiological factors were chronic obstructive pulmonary disease (10.6%), congenital heart disease (14.6%), idiopathic pulmonary hypertension (5.8%), and chronic thromboembolic pulmonary hypertension (3.8%). Only one of two patients with pulmonary artery hypertension was receiving PH specific therapies. The use of combination therapy was negligible and PH-specific therapies were prescribed off-label to a small proportion of patients too.

Conclusion: PRO-KERALA is the first PH registry from South Asia and the second largest globally. Left heart diseases attribute to three fifths of patients with PH. Utilization rates of PH specific drug therapies are remarkably lower than the Western population.

1. Introduction

Pulmonary hypertension (PH), which is characterized by increased pulmonary vascular pressure affects 15–60 per million people worldwide [1]. Although the disease entity is relatively rare, the debilitating progressive nature of PH often leads to significant morbidity and mortality [2] [3]. Epidemiological data on PH are scarce from low and middle-income countries (LMICs) including India [4]. However, it is likely that PH is more prevalent in India compared to the developed countries due to the high prevalence of predisposing disease conditions such as rheumatic heart disease (RHD) [5], chronic obstructive pulmonary disease (COPD) and untreated congenital heart diseases [6]. In contrast, left heart diseases and relatively rare conditions such as idiopathic pulmonary arterial hypertension [7] are the main predisposing factors of PH in the developed countries.

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PH is often considered as a disease without much therapeutic options, especially in resource-poor settings. However, with the availability and increased affordability of newer pulmonary vasodilators in the management of at least type 1 PH, there is renewed interest in understanding more about the patterns of PH in LMICs. Disease registries are an efficient way to collect epidemiological data on etiological and diagnostic characteristics, and therapeutic practice patterns of disease conditions. Findings from the disease registries often help clinicians and policymakers to promote understanding about potential causes, identify associations, facilitate early and accurate diagnosis, assess the uptake of evidence based guideline recommendations and identify gaps in management.

With the larger goal of describing the real world situation in terms of pattern, treatment practices and clinical outcomes, we established a multi-center registry of PH, the PRO-KERALA registry, in Kerala, India. The baseline characteristics and practice patterns are described in this paper.

2. Materials and methods

The detailed methods of PRO-KERALA registry have been published elsewhere [8]. In brief, cardiologists, internists and chest physicians from different parts of the state of Kerala, India were contacted. Of the 77 hospitals across Kerala which consented to participate in the registry, 50 registered consecutive eligible patients (Online Supplementary material - Appendix I).

A simple, interviewer-administered, structured questionnaire was used to collect relevant data. (Online supplement, Appendix II). The questionnaire was designed to capture demographic characteristics, risk factors, family history and echocardiographic data. Details of PH specific pharmacotherapy were also collected. Trained echocardiography lab nurses or research nurses administered the questionnaire and gathered data through detailed chart review. All the patients included in the registry were actively followed-up at every three months using a structured questionnaire.

Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Trivandrum, was the coordinating center. All the data collectors were given training by the investigators. A detailed study manual with instructions to fill-in the questionnaire was also provided. An informed consent was obtained from all the patients before enrolment.

Approvals were obtained from the respective Institutional Ethics Committees (IEC) of the participating centers and by the independent IEC of the Cardiological Society of India, Kerala Chapter (Approval No: ECR/252/Indt/KL/2015) – dated 26/03/2014). The IEC of SCTIMST, also cleared the study, with the approval number SCT/IEC-596 April – 2014. The study was funded by the Kerala Chapter of the Cardiological Society of India (CSI-K). All consecutive adult patients (≥18 years of age) with PH as per the following definitions were included in the registry.

2.1. Definitions

Pulmonary hypertension was defined as follows:

1) Systolic pulmonary artery (PA) pressure of >50 mmHg obtained by echocardiography by the tricuspid regurgitation (TR) velocity jet method [8] in the absence of significant right ventricular outflow obstruction, as per the equation: PA = 4 $(V)^2$ + estimated RA pressure (Where PA = systolic pulmonary artery pressure, V = peak velocity of tricuspid regurgitation jet, RA = right atrial) OR
2) Mean pulmonary artery pressure > 25 mmHg obtained during cardiac catheterization. We used the WHO 2013 Nice classification to classify PH based on etiological origin (Table 1) [9].

Newly detected cases were defined as pulmonary hypertension diagnosed within the last two months. All other cases were considered as previously diagnosed patients. The patients were followed-up during hospital visits or over telephone every, three months by the recruiting hospital or the coordinating center.

Etiological diagnosis was done based on standard criteria. All the patients underwent detailed echocardiographic evaluation by assessment of diastolic function by left ventricular inflow velocities and systolic function by Simpsons' method. The practicing cardiologists

Table 1
WHO 2013 Nice classification of pulmonary hypertension [9].

Group 1	Pulmonary arterial hypertension	1.1 Idiopathic PAH	
		1.2 Heritable PAH	1.2.1 BMPR2
			1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3.1 **1.2.3 Unknown**
		1.3 Drug and toxin induced	
		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′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
			1′′. Persistent pulmonary hypertension of the newborn (PPHN)
Group 2	Pulmonary hypertension due to left heart disease	2.1 Left ventricular systolic dysfunction	
		2.2 Left ventricular diastolic dysfunction	
		2.3 Valvular disease	
		2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	
Group 3	Pulmonary hypertension due to lung diseases and/or hypoxia	3.1 Chronic obstructive pulmonary disease	
		3.2 Interstitial lung disease	
		3.3 Others pulmonary disease with mixed restrictive obstructive patterns	
		3.4 sleep-disordered breathing	
		3.5 Alveolar hypoventilation disorders	
		3.6 Chronic exposure to high altitude	
		3.7 Developmental lung diseases	
Group 4	Chronic Thromboembolic pulmonary hypertension (CTEPH)		
Group 5	Pulmonary hypertension with unclear, multifactorial mechanisms	5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy	
		5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis	
		5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders	
		5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH	

BMPR2 = bone morphogenic protein receptor type 2; CAV1 = caveolin-1; ENG = endoglin; ALK-1 = activin receptor-like kinase-1; SMAD9 = mothers against decapentaplegic 9; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension.

always performed the echocardiography. Additionally, tissue Doppler velocity assessment was also done (E/e). All patients with established coronary artery disease underwent coronary angiogram and the left ventricular end diastolic pressure was directly measured. Chronic thromboembolic pulmonary hypertension (CTEPH) was diagnosed based on contrast computed tomography pulmonary angiogram ($n = 77$). Similarly, all patients who were diagnosed to have Group 3 PAH underwent pulmonary function test and evaluation by chest physicians before confirming the diagnosis ($N = 266$). Genetic testing was however not routinely done in our clinical settings. Similarly, vasodilatory testing for pulmonary vasoreactivity was done only in very few patients as inhaled Nitric Oxide was available at only one center.

2.2. Data management and analyses

Data were captured using the structured questionnaire. Data queries were generated periodically and sent to the respective sites for early resolution. The coordinating site staff provided periodic telephone feedback to resolve the data queries to the site staff. They conducted periodic monitoring visits (once in three months) to check the validity of the data. After clearing all data queries, a database lock was employed to finalize the baseline data set for statistical analyses.

Data were presented using summary statistics. The categorical variables are presented as proportions and continuous variables as means with standard deviation (SD). All analyses were carried out using Stata 12 (StataCorp, College Station, TX, USA).

3. Results

3.1. General characteristics of the study population

During the one-year study period, 2003 patients were enrolled into the registry (Fig. 1). All patients included in the registry satisfied either the echocardiography or cardiac catheterization based criteria. Discrepant cases (those who had >50 and <25 mmHg pulmonary artery pressure based on echocardiography and cardiac catheterization based criteria, respectively) were excluded from the registry ($n = 2$). The mean right ventricular systolic pressure in the whole population was 68.2 (SD = 17.9) mmHg. Women comprised 52% of the study population (Table 2). Eighty percent of patients were newly diagnosed while the remaining were on follow-up for some time. The study population was mostly middle aged with mean age of 56 (SD = 16.1) years.

3.2. Types of PH and etiology

Majority of the study participants (59%) belonged to group 2 of the WHO 2013, Nice classification. While 21.2% patients belonged to group 1, 13.3%, 3.8% and 2.4% belonged to group 3, 4 and 5, respectively (Table 2). The mean age was 63 years in group 3 participants, while it

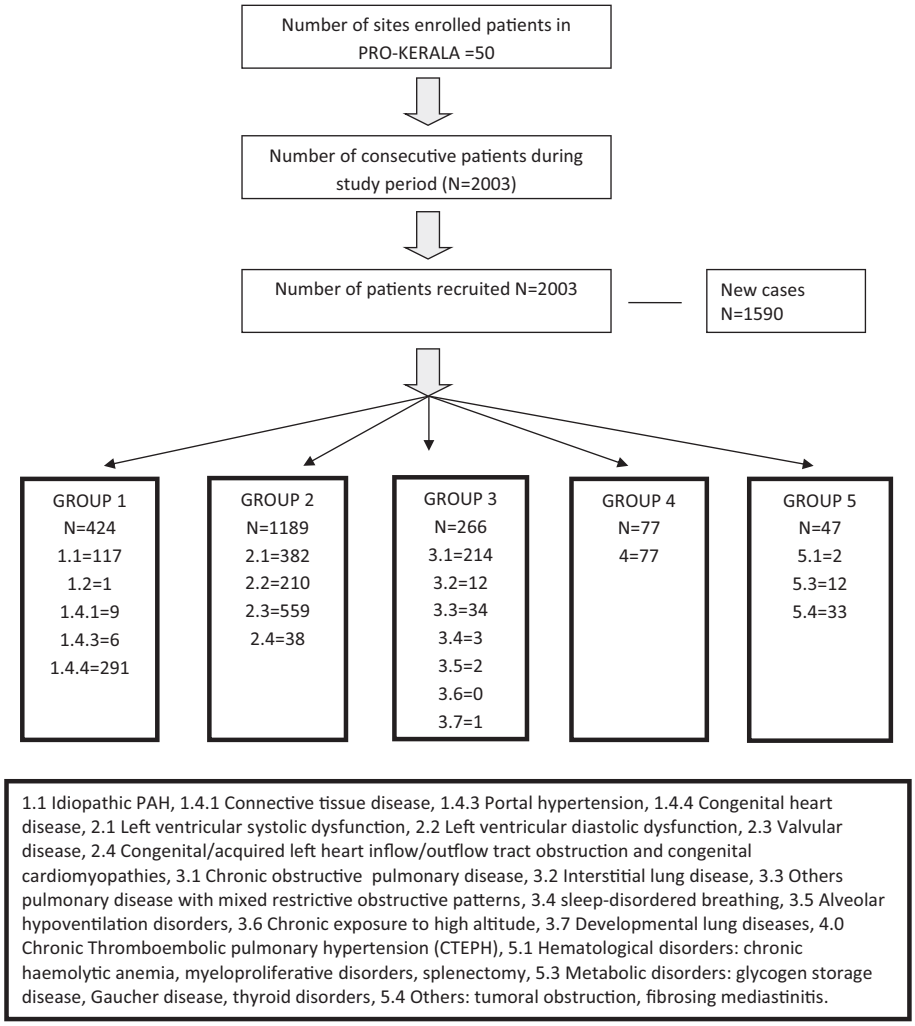

Fig. 1. The study cohort.

Table 2
Characteristics of PRO-KERALA registry patients.

	Men ($N = 963$)	Women ($N = 1040$)	Total ($N = 2003$)
Age, mean (SD)	58.4 (14.6)	53.6 (17.0)	55.9 (16.1)
PH category, n (%)			
Group 1	133 (13.8)	291 (27.9)	424 (21.2)
Group 2	623 (64.7)	566 (54.4)	1189 (59.4)
Group 3	158 (16.4)	108 (10.4)	266 (13.3)
Group 4	30 (3.1)	47 (4.5)	77 (3.8)
Group 5	19 (2.0)	28 (2.7)	47 (2.4)
Newly diagnosed, n (%)	792 (82.2)	798 (76.9)	1590 (79.5)
Symptoms at diagnosis, n (%)			
NYHA 1	45 (4.7)	61 (5.9)	106 (5.3)
NYHA 2	623 (64.7)	672 (64.6)	1295 (64.6)
NYHA 3	246 (25.6)	259 (24.9)	505 (25.2)
NYHA 4	49 (5.1)	48 (4.6)	97 (4.8)
Current symptoms, n (%)			
NYHA 1	45 (4.7)	58 (5.6)	103 (5.1)
NYHA 2	564 (58.6)	604 (58.1)	1168 (58.3)
NYHA 3	307 (31.9)	319 (30.7)	626 (31.3)
NYHA 4	46 (4.8)	59 (5.7)	105 (5.2)
Family history of PH, n(%)	11 (1.4)	10 (1.0)	21 (1.1)
Heart rate, mean (SD)	82.5 (17.7)	84.2 (17.2)	83.3 (17.5)
SBP, mean (SD)	129.2 (20.5)	129.6 (21.9)	129.4 (21.3)
DBP, mean (SD)	81.1 (8.2)	81.1 (8.5)	81.0 (8.3)
SPO2, mean (SD)	95.8 (4.3)	95.1 (4.6)	95.5 (4.5)
BMI, mean (SD)	23.5 (4.1)	23.0 (4.7)	23.2 (4.4)
Right heart failure, n (%)	199 (20.7)	172 (16.6)	371 (18.5)
RVSP, mean (SD) (mmHg)	66.7 (16.3)	69.6 (19.2)	68.2 (17.9)

PH = pulmonary hypertension, NYHA = New York Heart Association, SBP = systolic blood pressure, DBP = diastolic blood pressure, SPO2 = arterial saturation obtained by pulse oximetry, BMI = body mass index, RVSP = right ventricular systolic pressure.

was 44 years in group 1. The gender distribution of participants in each disease group and their corresponding mean ages are presented in Fig. 2.

One of four study participants (27%) reported PH related to left sided valvular heart disease. Chronic obstructive pulmonary disease was the main etiological factor in 10.6% cases, whereas congenital heart disease was reported in one of seven study participants (14.6%). Idiopathic pulmonary hypertension (IPAH) was reported in one of 20 study participants (5.8%). Thromboembolic pulmonary hypertension accounted for 3.8% of the patients, while other conditions including PH due to chronic kidney disease and PH due to multifactorial mechanisms were relatively rare with a prevalence of <2%. PH attributable to heritable, drug and toxin induced and systemic disorders were not reported in the study population (Fig. 2).

3.3. Other clinical characteristics

Right heart failure was reported in 18.5% of the population. At the time of diagnosis of PH, 30% of the study participants reported symptoms of NYHA class 3 or more.

3.4. Prescription patterns of PH specific drugs

Very few patients underwent hemodynamic testing prior to being initiated on PH specific therapy. Calcium channel blockers were prescribed to 4.3% of the study population. The details of other PH specific therapies are illustrated in Fig. 3. Patients who were using phosphodiesterase type 5 (PDE5) inhibitors (sildenafil and tadalafil) were analyzed together and compared with those patients who were using endothelin receptor antagonists (ERAs), Bosentan and Ambrisentan. PDE5 inhibitors were used by 17.1% of patients, while the proportion of patients on ERAs was only 2.3%. More than half (55%) of patients in Group 1 category were using some form of PH specific therapy, while only 4.4% of patients in Group 2 were taking such therapies. The usage of PH specific therapies were 25.2%, 39.3% and 11.8%, respectively among patients with group 3, 4 and 5 PH categories. Detailed data on the usage of the drugs in each patient group are presented in Fig. 3.

4. Discussion

PRO-KERALA is the first multi-centric registry of patients with PH from India. This is also the second largest registry of PH globally, with 2003 patients. Of all the existing PH registries, the US REVEAL [3] recruited more patients than PRO-KERALA. The COMPERA registry which is an ongoing multicentric European registry planning to recruit 9000 patients, has reported the data of 1283 patients so far [10]. All patients in PRO-KERALA are registered within one year, while the duration of recruitment was longer in other registries [4] [10]. In PRO-KERALA, we used a broader echocardiography defined entry criteria instead of the resource-intensive cardiac catheterization based definition.

Even though direct invasive measurement of PA pressure is the gold standard for the diagnosis of PH, Doppler echocardiography-based estimates have shown good correlation with direct measurements [11] [12] [13]. Additionally, echocardiography-based registries in the LMICs were found to be useful in describing patient characteristics as in the PAPUCO registry of sub-Saharan Africa [4] [14]. In order to initiate a registry of PH in low-resource settings, echocardiography-based definition is more practical and accessible given its convenience and affordability.

The patients in PRO-KERALA are middle aged with no sex-predominance. The mean age of PRO-KERALA participants is higher than that of most of the international registries [15]. However, it should be noted that PRO-KERALA recruited only adult patients above the age of 18 years into the registry. The patients in the PAPUCO registry had a mean age of 48 years [4]. Various other registries report mean age ranging from 36 to 65 years for idiopathic PH [15] which is comparable to the mean age of 44 years for IPAH subgroup in our study. Although the mean age of patients in the first PH registry (US-NIH registry) was 36 years [16], recent data show that PH is also frequently diagnosed in elderly patients [7]. There is no clear gender predominance in PRO-KERALA as compared to many other international registries. For

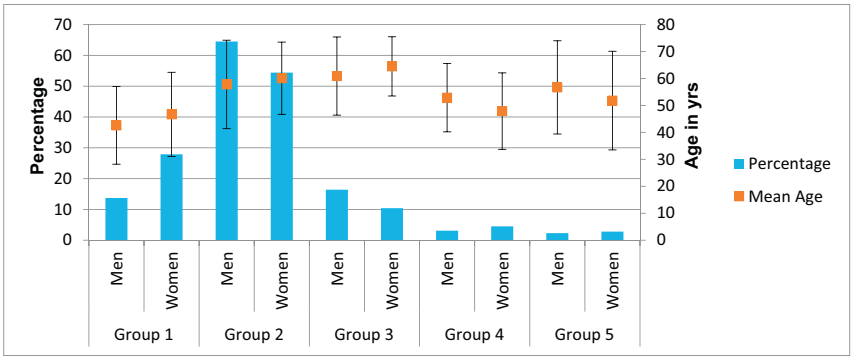

Fig. 2. Gender wise distribution of PRO-KERALA registry participants and their mean age.

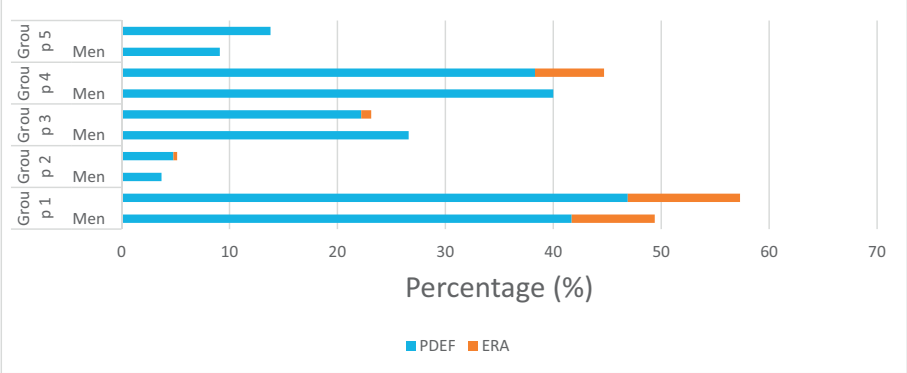

Fig. 3. Prescription pattern of pulmonary hypertension specific therapies in PRO-KERALA registry.

example, women comprised of nearly two thirds of the study population in the ASPIRE [17], PAPUCO [4] and the Swiss registries [18]. Majority of patients in PRO-KERALA report left heart disease as etiological factor, which is relatively less prevalent among women in India [19] [20] and may be one of the potential reasons for not showing female gender predominance.

While most of the other registries recruited only idiopathic PH or group 1 PH, PRO-KERALA included all consecutive PH patients with different disease etiologies. Majority of the epidemiological studies on PH focused on Group I PAH [7] while a few of them included CTEPH or Group 4 cases also [21]. Disease registries covering the whole spectrum of PH as in the current study are rare [17]. The European COMPERA [10]) and the PAPUCO are the only registries that covers the entire spectrum of PH. Of the 1283 cases of PAH reported from COMPERA, 800 cases were of IPAH(66%), and the rest were of other forms of PAH [10].

PRO-KERALA shows predominance of PH due to left heart disease. For example, one of four study participants reported left heart disease with valvular disease etiology, whereas only one in twenty have idiopathic PH. PAPUCO reported almost similar findings as in our study — 16% in Group I, 69% in Group 2, 11% in Group 3, 2% each in group 4 and 5 respectively. Most of the international registries report >30% prevalence of idiopathic PH [22] [23] [24] [25] [21] [10], while it is only 5% in PRO-KERALA. However, the international registries mostly include only group 1 category of patients [7].

In PRO-KERALA, PH due to valvular heart disease is the most common etiological condition, and it probably reflects the relatively high prevalence of rheumatic heart disease in India [26]. Additionally, several patients with valvular heart disease may not have been promptly treated in a timely fashion in resource-poor settings. Representative data from multiple geographical regions in India are needed to understand the distribution and etiological factors of PH at the national level.

There is no data on incidence of PH in India. If we indirectly estimate the annual incidence of PH in Kerala, based on the new cases (80% of PRO-KERALA participants) detected during the one-year period of registration, it would be equivalent to 48 per million adult population. This may be a gross underestimate, as the coverage is not 100% during the registration year, and under diagnosis is a common issue in low-resource settings. The estimated incidence of PH in the Spanish REHAP registry [21] is only 3.7 per million adult population per year, and it is remarkably lower than the estimate from PRO-KERALA.

Treatment strategies using PH-specific therapies are probably underused in PRO-KERALA participants. Only a few patients received calcium channel blockers, PDE5 and ERAs. Non-availability and poor access to facilities for cardiac catheterization and pulmonary vasodilatory testing in most parts of India may be one of the contributing reasons for inadequate initiation of PH specific therapies. For example, nitric oxide was available in only one center in Kerala at the time of enrollment, and it was in the private sector. Another reason for the low rate of prescription of PH specific therapies (both PDE5 inhibitors and ERAs) may be the cost of these drugs. The monthly cost of therapy with Sildenafil will come to 30 US Dollars, while dual therapy (Tadafil + Ambrisentan) will cost around 100 Dollars. Importantly, vast majority of patients with PH in India cannot afford such therapies as they live with an dispensable income of <2 US Dollars per day. Long-term mortality data from this cohort of PROKERALA registry patients will provide important information on the role of these therapies on outcome measures and including mortality benefits.

Although the survival benefits of PH specific therapies are yet to be established in situations other than Idiopathic PH, they are prescribed off-label for other types of PH. It is therefore important to sensitize the practitioners with the available evidence and encourage them to follow therapies supported by clear data. Quality improvement programs may help in improving the practice of evidence based treatment of PH in similar settings.

5. Conclusions

PRO-KERALA is one of the largest PH registries globally, and it represents patients from Kerala, India. The patients in this registry are middle-aged with no gender predominance. Predominance of valvular disease etiology is evident in the PRO-KERALA registry. Utilization of PH-targeted therapies is much lesser in PRO-KERALA, and importantly, they are also prescribed off-label to a smaller proportion of patients. A quality improvement program among practitioners may help in improving the practice of evidence based therapies for PH. A national registry involving multiple geographical regions in India with standardized data collection methods and long-term follow-up are essential to understand the distribution and etiological factors of PH at the national level and to assess the role of PH specific therapies on survival.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.02.036.

Author contributions

SH, GS and JP had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KK, JM, AM and RGN were involved in planning the study, recruiting the patients, preparing the manuscript and reviewing it. AGK, TAV, RG, EP, SMA, ASR and MC were involved in planning the study and collecting the data. SH, GS and JP are the guarantors of the paper.

Conflict of interest

None of the authors have any conflict of Interests to declare.

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