RESEARCH ARTICLE

National Institute Pulmonary Hypertension Registry (NIPHeR): Insights from the first pulmonary hypertension registry of Pakistan

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Abstract

Objective: To analyse the characteristics, management and outcomes of patients with pulmonary hypertension from a dedicated registry.

Method: The retrospective study was conducted at the Pulmonary Hypertension Clinic of the National Institute of Cardiovascular Disease (NICVD), Karachi from November 2021 to July 2023, and comprised data of patients above eighteen years diagnosed with pulmonary hypertension. Data was retrieved from the National Institute Pulmonary Hypertension Registry (NIPHeR), and was categorised as per the 6th World Symposium on Pulmonary Hypertension 2018 classification into groups 1-5. Patient data was collected using a Proforma. Data was analysed using SPSS 27.

Results: Of the 145 patients with mean age 43.10±14.71 years, 92(63%) were females. Group 4 had the most number of patients 50 (34.5%). Dyspnoea and fatigue were the most common complaints, lasting a mean duration of 22.71±29.11 months. The majority 94 (65%) of patients had New York Heart Association Functional Class III or IV, but within 6 months of treatment, the number went down to 72(49.6%). Mortality was reported in 9 (6.2%) cases, and it was significantly associated with Group 4 ($p<0.05$). Factors significantly associated with increased mortality were Group 4 PH (Pulmonary hypertension associated with pulmonary embolism), an electrocardiographic evidence of right ventricle hypertrophy (RVH) along with severe or persistent right ventricle dysfunction, and use of Endothelin receptor antagonists (ERA) as monotherapy, while there use in combination with phosphodiesterase 5 (PDE5) inhibitors was associated with decreased mortality ($p<0.05$).

Conclusion: The importance of early diagnosis and appropriate management of pulmonary hypertension cannot be overemphasized. The National Institute Pulmonary Hypertension Registry could serve as a vital tool for understanding regional trends and guiding future clinical practice and research in pulmonary hypertension.

Keywords: Pulmonary hypertension, Registry, Pulmonary artery, Echocardiography, Vasodilator agents, Mortality.

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Introduction

Pulmonary hypertension (PH) is a diverse disease caused by high pressure in the pulmonary arteries, defined as having a resting mean pulmonary artery pressure (mPAP) >20mmHg measured by right heart catheterisation (RHC). PH is categorised into different types based on specific haemodynamic parameters. Precapillary PH is defined as a mean pulmonary artery pressure (mPAP) >20mmHg, pulmonary artery wedge pressure (PAWP) ≤15mmHg, and pulmonary vascular resistance (PVR) >2 Wood units (WU). Isolated postcapillary PH (IpcPH) is characterised by an mPAP >20mmHg, PAWP >15mmHg, and PVR ≤2 WU, while combined postcapillary and precapillary PH (CpcPH) is defined as an mPAP >20mmHg, PAWP >15mmHg, and PVR >2 WU. Exercise PH is identified by mPAP to cardiac output (mPAP/CO) slope between rest and exercise >3mmHg/L/min.[1-5]

Global pulmonary arterial hypertension (PAH) prevalence is estimated at 15-60 per million adults, with middle- and low-income regions (MLIRs) experiencing a much higher disease burden than high-income regions (HIRs), with the estimated incidence recently reported to be 48 per 1 million people in 2015 by the Pulmonary hypertension Registry Of Kerala (PROKERALA) in India. Key contributors in MLIRs include rheumatic heart disease, untreated congenital heart disease, left heart disease (due to coronary artery disease and unrecognised hypertension), lung diseases linked to tuberculosis, smoking, air pollution, schistosomiasis and human immunodeficiency virus (HIV) infection (Africa), and idiopathic PAH (IPAH) driven by large

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populations. Despite the rising burden, currently, there are only a few registries in low- and middle-income countries (LMICs) that are committed to gathering PH data, mainly the Asian Pulmonary Hypertension Registry (Asian countries), Pan African Pulmonary Hypertension Cohort (PAPUCO) (sub-Saharan Africa), PROKERALA (India), Ukrainian Pulmonary Hypertension Registry, Brazilian Pulmonary Hypertension Registry (BPHR), Thai Pulmonary Hypertension Registry, and Global Alliance for Pulmonary Hypertension (GAP) registry (LMICs). Hence, there is a dearth of data on the incidence, prevalence and cause of PH, highlighting the critical need for better healthcare infrastructure and timely interventions in MLIRs.[5-9]

The 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018 updated the PH classification into five groups.[5] Group 1 (PAH) is the most aggressive, affecting younger individuals, particularly females, and comprises idiopathic/heritable, drugs/toxins, PH associated with congenital heart disease, connective tissue disease, HIV/schistosomiasis, portal hypertension, and persistent pulmonary hypertension (PPHN). Group 2 (PH caused by left heart disease) includes left ventricular (LV) systolic/diastolic dysfunction, valvular disease, congenital/acquired left heart inflow/outflow obstruction, and cardiomyopathies. Group 3 (PH caused by lung disease/hypoxia) occurs in the setting of chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), or hypoxia secondary to high altitude, sleep-disordered breathing, or alveolar hypoventilation disorders.[10] Group 4 (chronic thromboembolic pulmonary hypertension [CTEPH]) involves an obstruction in the pulmonary arteries due to emboli. Group 5 (PH with unclear multifactorial mechanisms) has a multifactorial aetiology, including haematological, systemic/metabolic disorders, and secondary to drugs and miscellaneous causes, such as end-stage renal disease (ESRD).[1,3,6,11]

PH can initially present with non-specific symptoms, such as light-headedness and fatigue. Patients usually seek medical attention when they develop respiratory or cardiac symptoms, like progressive dyspnoea, chest pain, haemoptysis, syncope, or palpitations. Signs of right ventricular failure (RVF) may be present. Cardiac examination may reveal a loud P2, S3 gallop, or tricuspid (TR) or pulmonary (PR) regurgitation murmur.[1,2,5]

A plain chest radiograph (CXR) is a vital initial tool for evaluating PH with 97% sensitivity and 99% specificity. The classic findings include enlarged central pulmonary arteries (>15mm in women, >16mm in men) and pruning of peripheral arteries, with disease progression resulting in right atrial enlargement and ventricular dilation, indicated by a cardiac silhouette with a prominent right heart border. CXR can also aid in evaluating the pulmonary cause of PH. In the case of mild PH, it can be normal.[12]

A transthoracic echocardiography is a valuable non-invasive tool in detecting PH, primarily using the Bernoulli equation to calculate pulmonary artery systolic pressures (PASP or sPAP) from tricuspid regurgitation velocity (TRV) that, if done by experienced sonographer, can be detected in about 90% of the cases with a sensitivity of 82% and specificity of 80%. Additional findings include septal distortion, reduced LV volumes, and "D-shaped" LV indicating chronic RV pressure overload in PH, leading to RV hypertrophy. RV size, PA pressure and echo saline bubble study for excluding right to left shunting are also valuable in PH.[13,14]

RHC is the gold standard for PH diagnosis,[15,16-18] defining PH as mPAP >20mmHg, PCWP <15mmHg and PVR >2WU. Vasoreactivity testing (inhaled nitric oxide [NO], adenosine, iloprost, or intravenous [IV] epoprostenol) can detect acute pulmonary vasodilator responsiveness in PAH patients. This test helps identify patients who may benefit from calcium channel blocker (CCB) therapy, a specific treatment option for acute responders in PAH.[4,19] Computed tomography pulmonary angiogram (CTPA) is a non-invasive imaging modality for identifying morphological changes, like PA or RV dilation, linear PA calcifications, and pulmonary thromboembolic disease. Cardiopulmonary exercise testing, or a 6-minute walk test (6MWT), can identify the severity of exercise limitations and treatment response. Electrocardiography (ECG) signs of RV hypertrophy or failure (RVH or RVF), right axis deviation (RAD), right bundle branch block (RBBB), peaked P-wave on ECG (P-pulmonale), prolonged corrected QT interval (QTc), or S1Q3T3 pattern (S wave in lead 1, Q wave in lead 3 and inverted T wave in lead 3) (in pulmonary embolism [PE]) may be present. Additional investigations include arterial blood gas (respiratory failure) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) (RV overload), cardiac magnetic resonance imaging (MRI), RV strain imaging or 18F-flourodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) (to differentiate CTEPH).[1,19]

PH is managed via a multidisciplinary approach that takes into account the PH group, clinical features, like New York Heart Association- Functional Class (NYHA FC) and 6MWT, and laboratory features, like NT-proBNP, haemodynamics, and overall risk stratification. Supportive measures include rehabilitation, aerobic exercise, influenza vaccination, smoking cessation, contraception, psychosocial support, and patient education.[2,4,7] Medical treatments include diuretics, anticoagulation and pulmonary vasodilator drugs.[5,19] The Food and Drug Administration (FDA) has

approved 14 drugs to treat PH, including CCB, prostanoid therapies (prostacyclin analogues and prostacyclin-receptor agonist-selexipag), endothelin receptor antagonist (ERA) (ETA and ETB) (Endothelin receptor A and B antagonist), phosphodiestrase-5 inhibitor (PDE5), and soluble guanylyl cyclase stimulator (Riociguat). Despite new treatments, managing PH is complex with high mortality and morbidity. Lung transplantation is an option for patients with a high-risk diagnosis, comorbidities, or poor prognosis features not responding to vasodilator treatment. However, lung transplantation has high mortality and morbidity.[9,19,20]

PH registries are working globally to collect data and aid physicians and researchers in understanding the disease. However, Pakistan lacks a PH database. To fill this gap, the National Institute Pulmonary Hypertension Registry (NIPHeR) was established in November 2021 in collaboration with the pulmonary hypertension clinic (PHC) at the National Institute of Cardiovascular Disease (NICVD) in Karachi. NIPHeR is the first PH registry in the region and has already enrolled 450 patients from across Pakistan, including 200 children and 250 adult PH patients. The registry tracks regional PH data and aims at initiating an advocacy movement, with the ultimate goal of developing local PH guidelines in Pakistan.

The current study was planned to use NIPHeR data to analyse the characteristics, management and outcomes of PH patients in Pakistan.

Patients and Methods

This retrospective study was conducted after ethical approval from November 2021 to July 2023 at the pulmonary hypertension clinic (PHC) of NICVD, Karachi, and comprised data prospectively collected from the National Institute Pulmonary Hypertension Registry (NIPHeR). WHO sample size calculator version 2.0 was utilized to calculate the sample size.[21] Considering the study by Radchenko GD et al.[22] that reported 11% mortality in PH patients. At 95% confidence interval (CI) and 50% relative precision, the minimum required sample size was calculated to be 125, hence considering the 15% expected dropout rate at 3-6 months follow-up, a total of 145 patients were recruited. The data was collected utilizing Proforma from patients visiting the PHC. The patients above eighteen years of either sex diagnosed with any group of pulmonary hypertension were recruited. Individuals with active lung infections, malignancies, or unwillingness to participate were excluded.

PH was defined as echocardiographically measured pulmonary artery systolic pressure (PASP) ≥25mmHg at rest. The severity of PH was classified as mild (PASP 25-40mmHg), moderate (PASP 41-55mmHg) and severe (PASP ≥55mmHg). Data was categorised as per the 6th World Symposium on Pulmonary Hypertension 2018 classification into groups 1-55; Group 1 had patients with PAH, Group 2 had those with PH due to left heart disease, Group 3 had patients with PH due to lung disease, hypoxia, Group 4 patients had had PH associated with pulmonary embolism, and Group 5 had those having PH with unclear multifactorial mechanisms. Group 4 contained PH patients admitted or followed for acute or chronic pulmonary embolism (pulmonary hypertension associated with pulmonary embolism.

Data was gathered using a proforma, and included demographic information, comorbidities, NYHA FC, symptoms, electrocardiography (ECG), CXR, echocardiography, spirometry, arterial blood gas (ABG), complete blood count (CBC), urea, creatinine and electrolytes (UCE), coagulation profile, liver enzymes, viral markers, thyroid profile, autoimmune profile, cardiopulmonary exercise testing (CPET), polysomnography, pulmonary function test (PFT), ultrasound abdomen and Doppler ultrasound of the lower limb, computed tomography (CT) scan of chest with high-resolution contrast (HRCT), CT pulmonary angiogram (CTPA), management, hospital admission, intensive care unit (ICU) or mechanical ventilation (MV) need, and outcomes. The investigations were customised based on the patient's clinical context. Prior written informed consent had been obtained from every patient. Follow-up was done every 3-6 months, with 6MWD, NYHA FC and PASP measurement used to assess treatment response.

Data was analysed using SPSS 27. Quantitative variables were tested for normality of distribution with Shapiro-Wilk test, and, based on the distribution, these variables were represented by mean±standard deviation or median with interquartile range (IQR), while qualitative data was represented by frequencies and percentages. Chi-square test was used to assess association involving PH groups and categorical variables, while one-way analysis of variance (ANOVA) was used to compare the mean values. $P<0.05$ was considered significant.

Results

Of the 145 patients with mean age 43.10±14.71 years, 92(63%) were females. Group 4 had the most number of patients 50(34.5%), followed by Group 1 45(31.03%), Group 3 33(22.75%) and Group 2 17(11.7%). There was no patient in Group 5. The female gender prevailed in Groups 1, 2 and 3, while the male gender dominated Group 4 ($p<0.001$). PH severity in terms of mean resting PASP was the highest in Group 1 (74.71±26.38) ($p<0.05$), while in terms of

Table-1: Comparison of baseline characteristics and right heart catheterization data among pulmonary hypertension groups (n=145).

Parameters	Pulmonary Hypertension groups				*p*-value
	Group 1- PAH	Group 2- PH due to left heart disease	Group 3- PH due to lung disease/Hypoxia	Group 4- Pulmonary Hypertension associated with pulmonary embolism	
n (%)	45 (31)	17 (12)	33 (23)	50 (34)	
Gender, Female	37 (82)	14 (82)	21 (64)	20 (40)	<0.001
Symptoms					<0.05
Dyspnoea	43 (96)	17 (100)	33 (100)	50 (100)	
Fatigue	36 (80)	9 (53)	28 (85)	38 (76)	
Cough	32 (71)	9 (53))	25 (76)	32 (64)	
Light Headedness	33 (73)	7 (41)	16 (49)	33 (66)	
Syncope	33 (73)	7 (41)	15 (46)	29 (58)	
Chest Pain	19 (42)	5 (29)	11 (33)	15 (30	
NYHA Functional Class at presentation					<0.001
I	1 (2.2)	1 (5.9)	0 (0)	0 (0)	
II	19 (42.2)	3 (17.6)	16 (48.5)	11 (22.0)	
III	23 (51.1)	12 (70.6)	16 (48.5)	24 (48.0)	
IV	2 (4.4)	1 (5.9)	1 (3.0)	15 (30.0)	
Pulmonary Hypertension Severity [n (%)]					<0.05
Severe	36 (80)	11 (65)	21 (64)	24 (48)	
Moderate	6 (13)	4 (24)	7 (21)	12 (24)	
Mild	3 (6.7)	2 (12)	5 (15)	14 (28)	
Severity of Right Ventricular dysfunction					<0.05
Severe	5 (11)	5 (29)	3 (9.1)	7 (14)	
Moderate	17 (38)	1 (5.9)	15 (46)	27 (54)	
Mild	8 (18)	3 (18)	4 (12)	5 (10)	
NYHA Functional Class at six months					0.081
I	2 (4.4)	1 (5.9)	0 (0)	5 (10.0)	
II	25 (55.6)	5 (29.4)	10 (30.3)	25 (50.0)	
III	13 (28.9)	10 (58.8)	16 (48.5)	15 (30.0)	
IV	5 (11.1)	1 (5.9)	7 (21.2)	5 (10.0)	
Hospital Admission					<0.001
n (%)	24 (60)	10 (62)	12 (44)	43 (88)	
ICU Admission					<0.001
n (%)	4 (22)	1 (11)	0 (0)	25 (66)	
Outcome					<0.05
Expired	2 (4.4)	1 (5.9)	2 (6.1)	4 (8)	
Under treatment	29 (64)	9 (53)	22 (67)	42 (84)	
Referred to other specialty	11 (24)	6 (35)	7 (21)	0 (0)	
Lost to follow-up	3 (6.7)	1 (5.9)	2 (6.1)	4 (8)	
Parameters	**Baseline characteristics (Mean±SD)**				
Age (years)	36.24 ± 11.27	41.76 ± 14.86	46.91 ± 12.24	47.18 ± 16.79	<0.001
BMI, Kg/m^2	23.82 ± 5.39	26.05 ± 4.73	27.68 ± 6.73	25.83 ± 5.03	<0.05
Duration of Symptoms, months	32.82 ± 32.01	18.25 ± 21.85	28.54 ± 31.84	11.27 ± 22.23	<0.001
Resting Mean PASP at presentation, mmHg	74.71 ± 26.38	56.47 ± 21.63	64.12 ± 26.17	56.98 ± 26.84	0.007
Resting Mean PASP at six month follow up, mmHg	73.54 ± 31.39	58.67 ± 28.61	73.38 ± 33.42	46.71 ± 28.22	<0.05
	Right Heart Catheterization (RHC) data (Mean±SD)				
RHC done n (%)	22 (50)	4 (24)	3 (9.1)	4 (8)	<0.001
Hyperoxia Test done n (%)	7 (16)	1 (5.8)	1 (3.0)	0 (0)	
PA Pressures, Mean ± SD, mmHg	57.95 ± 22.55	60.00 ± 10.00	50.00 ± 30.41	69.00 ± 29.69	
PCWP Mean ± SD, mmHg	12.50 ± 4.23	20.51 ± 2.20	13.00 ± 7.07	12.01 ± 2.11	
PVR, Mean ± SD, WU/m^2	17.71 ± 11.68	-	16.63 ± 23.44	18.40 ± 1.41	
SVR, Mean ± SD, WU/m^2	31.19 ± 11.08	-	27.06 ± 23.20	26.70 ±15.83	

No Group 5 pulmonary arterial hypertension (PH) patient was identified; PAH: Pulmonary arterial hypertension, NYHA: New York Heart Association, BMI: Body mass index, PASP: Pulmonary artery systolic pressure, RHC: Right heart catheterisation, PCWP: Pulmonary capillary wedge pressure, PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance.

percentage of patients, the severity was the highest in Group 1 PH 36(80%), followed by Groups 2, 3 and 4 (p<0.05). Fatigue, dyspnoea and light-headedness were the primary symptoms in all the groups, with an average duration of symptoms of 22.71±29.11 months, and the longest duration was observed in Groups 1 and 3 (p<0.001).

Among comorbidities, obesity was significantly related with Group 3 having mean body mass index (BMI) 27.68±6.70 (p<0.05), while immobilisation was a significant risk factor identified with Group 4 (p<0.05). Group 3 patients had a lower mean oxygen saturation (88.88±10.13) (p<0.05). The mean left atrial (LA) volumes were significantly higher among Group 2 patients (38.26±14.26) (p<0.05). The mean haematocrit concentration was significantly higher in Group 3 (41.22±10.50) (p<0.05) (Table 1).

Medical treatment, including diuretics and heart failure medications, was given to all the groups, with Group 4 receiving the least diuretics 17(35%) (p<0.001). In contrast, anticoagulation was almost exclusively used in Group 4 47(94%) (p<0.001) and long-term oxygen therapy (LTOT) was given more frequently to Group 3 patients 13(42%) (p<0.001). Further, 76 (52.4%) patients were put on pulmonary vasodilators, with large proportion shared by Group 1 38(84%) and Group 3 19 (58%) (p<0.001). The most commonly used pulmonary vasodilators were Bosentan n=74 (51%) and Sildenafil n=42 (29.2%), with 'n=35 (24.1%) patients receiving only single pulmonary vasodilator, and

Table-2: Management data across pulmonary hypertension (PH) groups.

Parameters	Pulmonary Hypertension groups				*p*-value
	Group 1- PAH	Group 2- PH due to left heart disease	Group 3- PH due to lung disease/Hypoxia	Group 4- Pulmonary Hypertension associated with pulmonary embolism	
n (%)	45 (31)	17 (12)	33 (23)	50 (34)	
CPAP/LTOT	9 (21)	2 (12)	13 (42)	4 (8.5)	<0.001
Pulmonary Vasodilator Therapy					
Pulmonary Vasodilator given	38 (84)	8 (47)	19 (58)	11 (22)	<0.001
Monotherapy	12 (27)	5 (29)	13 (39)	5 (10)	<0.05
Polytherapy (≥2)	26 (58)	3 (18)	6 (18)	6 (12)	<0.001
ERA (Bosentan)	38 (84)	8 (47)	17 (52)	11 (22)	<0.001
PDE5 (Sildenafil)	26 (58)	3 (18)	8 (24)	5 (10)	<0.001
ERB+PDE5	26 (58)	3 (18)	6 (18)	5 (10)	<0.001
Prostacyclin Analogues	3 (6.7)	0 (0)	0 (0)	0 (0)	0.071
Guanylyl Cyclase stimulator	0 (0)	3 (6.0)	0.121		
CCB	1 (2.2)	1 (5.9)	0 (0)	0 (0)	0.260
Heart Failure Medications					
Diuretics/ACE Inhibitors/ARB	39 (89)	15 (88)	26 (78)	17 (35)	<0.001
Anticoagulation given	9 (20)	4 (24)	2 (6.1)	47 (94)	<0.001
Oral Anticoagulation	9 (20)	4 (24)	2 (6.1)	45 (90)	
Rivaroxaban	6 (13)	1 (5.9)	1 (3)	44 (88)	
Warfarin	3 (6.7)	3 (18)	1 (3.0)	6 (12)	0.281
IV or S/C Anticoagulation		0 (0)		36 (72)	<0.001
Heparin Infusion				21 (42)	
LMWH (Enoxaparin)				15 (30)	
Streptokinase				14 (28)	
Tissue Plasminogen Activator (tPA[9])				3 (6.0)	0.120
Intervention done	1 (2.2)	0 (0)	1 (3.0)	6 (12)	0.091
Septostomy	1 (2.2)	0 (0)	1 (3.0)	1 (2)	-
Intrapulmonary Arterial Thrombectomy		0 (0)		2 (4)	
IVC Filter placement				3 (6.0)	0.120
Surgical Management					-
ASD Closure	1 (2.2)		0 (0)		
Pulmonary Embolectomy		0 (0)		1 (2)	
Right Pulmonary Thromboendarterectomy				1 (2)	

PAH: Pulmonary arterial hypertension, CPAP: Continuous positive airway pressure, LTOT: Long-term oxygen therapy, ERA: Endothelin receptor antagonists, PDE5: Phosphodiesterase 5 inhibitors, CCB: Calcium channel blockers, ACE: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin receptor blockers, IV: Intravenous, S/C: Subcutaneous, LMWH: Low-molecular-weight heparin, tPA: Tissue plasminogen activator, IVC: Inferior vena cava. ASD: Atrial septal defect.

Table 3: Factors influencing prognosis in pulmonary hypertension (PH) patients.

Factors Influencing Changes in Functional Class	
Factors associated with worsening of functional class	• NYHA Functional Class III at presentation (p<0.001) • Need of long-term oxygen therapy (LTOT) during first six months of treatment (p<0.05) • Moderate to severe TR at presentation (p<0.05) • Group 3 PH (Pulmonary hypertension due to lung disease and/or hypoxia (p<0.001) • Murmur of TR at presentation (p<0.05) • Ascites at presentation (p<0.05) • Obstructive sleep apnoea (p<0.05)
Factors associated with improvement of functional class	• NYHA Functional Class II at presentation (p<0.001) • Hospital admission during six months of treatment (p<0.001) • Use of diuretics (p=0.07) • Use of vasodilator drugs (p<0.05) • No or mild TR at presentation (p<0.05) • Treated cases of Group 4 PH (Chronic thromboembolic pulmonary hypertension (p<0.001) • Use of Anticoagulation (p<0.05) • Use of Rivaroxaban (p<0.001), tissue Plasminogen activator (t (p=0.07), and Enoxaparin (p<0.05) (Only for Group 4 PH) • Deep vein thrombosis (p<0.001)
Factors associated with mortality in Pulmonary Hypertension patients	
Factors associated with increased mortality	Moderate to Severe Right ventricle Dysfunction at presentation (p<0.05) Persistent right ventricle dysfunction during treatment (p<0.05) ECG having signs of right ventricle hypertrophy (p<0.05) Group 4 PH (p<0.05) High mean pulmonary artery pressures (on cath) [PA pressures> 55 mmHg (p=0.09) Pulmonary vascular resistance (PVR)> 3 WI/m^2 (p<0.01) Use of pulmonary vasodilators as single therapy (ERA) (p<0.01)
Factors associated with decreased mortality	Use of pulmonary vasodilators as combination therapy (ERA+PDE5) (p<0.05)

NYHA FC: New York Heart Association functional class, TR: Tricuspid regurgitation, PVR: Pulmonary vascular resistance, ERA: Endothelin receptor antagonist, PDE5: Phosphodiestrase 5 inhibitors, ECG: Electrocardiogram.

n=41 (28.2%) getting combinations. Prostacyclin analogues and guanylyl cyclase stimulator were used in n=3 (2%) patients. Rivaroxaban was the most commonly used oral anticoagulants were used in n=52 (35%) patients, given primarily to group 4 patients n=44 (88% of Group 4 patients) and a small proportion (n=5) (13% of Group 1 patients) (p<0.001). Systemic anticoagulation was exclusively used in Group 4 (p<0.001). Deep vein thrombosis (DVT) (p<0.05), PE (p<0.05), and intra-cardiac thrombus were exclusively reported in Group 4 (p<0.01), and resolved in most patients by 6 months (Table 2).

The NYHA FC in majority patients was class III at presentation 75(51.7%), with number decreasing to 54(37.2%) at 6 months follow-up, while FC II at presentation was present in 49(33.7%) patients, which improved to 65(44.8%) at 6 months (p<0.001). Group 4 patients shared the largest proportion of NYHA FC 4 patients at presentation 15(78.9%), showing marked improvement at 6 months, with only 5 (27.8%) at FC 4 at 6 months. However, after 6 months, mean PASP (63.2±32.41) did not change significantly, while mean right atrial (RA) volume increased in all groups (40.67±10.75 at presentation vs. 51.5±10.42 at 6 months) (p<0.05). The left atrial (LA) volume was higher in Group 2 (p<0.05).

Group 4 patients had the highest number of ICU admissions (p<0.01) and the highest duration of hospital stay (p<0.05), while Groups 1 and 3 got the most specialist referrals (p<0.05). The overall mortality was 9(6.2%), which was highest in Group 4 patients (p<0.05).

Mortality was higher in females (p=0.09), uneducated people (p<0.05), and those in the 2nd, 3rd and 5th decades of life (p<0.05), with Group 4 having the highest mortality; 4(8%) (p<0.05). Mortality was linked to several factors, including findings of RVH (p<0.05), moderate-severe RV dysfunction (p<0.05), or persistent RV dysfunction after treatment (p<0.05), echocardiographic PASP ≥55mmHg (p=0.09), and PVR ≥3WI/m^2 on right heart catheterisation (p<0.05). The use of pulmonary vasodilator was associated with lower mortality (p<0.05). ERA used as monotherapy had higher mortality 8(88.9%) (p<0.01) vs. PDE5 alone 5(55.6%) (p=0.08) vs. ERA+PDE5 combination therapy 5(55.6%) (p=0.066) (Table 3).

Discussion

In the current study, Group 4 PH was the most commonly encountered, whereas other registries have reported predominantly Group 1.[19-26] The Saudi Arabia pulmonary hypertension registry (SAUDIPH) and Iranian PAH registries have reported PH in the third decade, which is similar to the current findings. However, the Collaborative registry of pulmonary hypertension in Argentina (RECOPILAR), The Registry to Evaluate Early and Long-term PAH Disease Management (US REVEAL), the Registry on clInical outcoMe and survival in pulmonary hypertension Groups (SIMURG), Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA-CHD), The United States Pulmonary Hypertension Scientific Registry (USPHSR), Swiss PH, and PRO-KERALA registries have reported PH in the fourth, fifth, and sixth decades.[22-26] The RECOPILAR and Adalimumab Biosimilar Patient Registry (ASPIRE) registries reported Group 4 PH in the fourth decade. In the current study, males predominated in Group 4 with 60%, while in all other groups, females dominated with 60%, similar to data from RECOPILAR, USPHSR, US REVEAL, SIMURG, Southern Brazil registry (RESPHIRAR study) and COMPERA registries.[17-19] The most common symptoms in the current study were dyspnoea and fatigue, followed by cough, light-headedness and syncope, similar to the RECOPILAR and RESPHIRAR registries.[22-24] Most patients in the current study had advanced NYHA FC (III/IV), as was the case in SIMURG (FC IV/III),[24] SAUDIPH (FC III/IV)(25), RECOPILAR (FC III/IV),[23] US REVEAL (FC III/IV), French Registry (FC III/IV),[26]

PRO-KERALA (FC II/III),[27] USPHSR (FC III/II)[28] and RESPHIRAR (FC II/III).[29] In the current study, the most frequently encountered arrhythmia was atrial fibrillation (8.7%), similar to the RECOPILAR registry.[23] Group 1 had the highest resting PASP in the current study, followed by Groups 3, 4 and 2, which is comparable to the results of the RECOPILAR registry.[6,23,24,29]

In the current study, 55% patients received pulmonary vasodilator therapy, which was associated with lower mortality (11.1%) compared to when no pulmonary vasodilator was used (88.9%) (p<0.05). However, the use of Bosentan alone had higher mortality (88.8%) than sildenafil alone (p<0.01) or a combination of both (p=0.06), which had lower mortality (55%).

The use of combined therapies for PH is becoming more common. The recommended combination for FC III and IV includes IV epoprostenol, Bosentan, and Sildenafil. Other combinations include newer drugs, such as Ambrisentan, Macitentan, Selexipag, Tadalafil and Riociguat. Although combination therapy might improve symptoms and FC, it does not confer any benefit over monotherapy in enhancing long-term survival.[9,19,30]

The European Society of Cardiology and European Respiratory Society (ESC/ERS) 2015 PH guidelines suggest using subcutaneous treprostinil, or intravenous Iloprost for patients with FC III/IV on an outpatient basis.[1,19] However, in Pakistan, only Bosentan and Benprost are approved by the Drug Regulatory Authority of Pakistan (DRAP)[31] for PH treatment (Pakistan, 2025), and most of the drugs mentioned in the guidelines are not available. In this study, 41% patients received anticoagulation therapy, similar to the rates seen in the RECOPILAR registry.[23] Only a small number of patients (1.4%) used CCBs, comparable to data from the USPHSR, COMPERA and PRO-KERALA registries.[6,27,28]

The prevalence of heart failure medication use was higher in the current patients (67.8%) compared to the PRO-KERALA registry (39.4%),[27] particularly for those in Groups 1, 2 and 3. A few patients from Groups 1 and 4 underwent interventional and surgical treatment, such as septostomy, atrial septal defect (ASD) closure, inferior vena cava (IVC) filter, intrapulmonary arterial thrombectomy, pulmonary embolectomy, and right pulmonary thrombo-endarterectomy. Furthermore, 15.2% of the patients received specific medical therapy, which included aspirin (21%), beta-blockers (4.8%), digoxin (2.8%), statins (2.1%), hydroxycholoroquine (HCQ) (1.4%), mineralocorticoid receptor antagonist (MRA) (1.4%), thyroxine, benzathine penicillin, febuxostat, insulin, and metformin (0.7%).

The current data revealed a one-year survival rate of 93.7%, which is consistent with COMPARE (90%), US REVEAL (91%), Ukrainian registry (93.3%) and SAUDIPH (96.6%). However, the one-year survival rate was lower in the Swiss, Spanish, Danish and European registries. The ASPIRE and Giessen Pulmonary Hypertension Registry registries reported higher mortality rates (12% and 14.5%, respectively) than the current study (6.2%).[32]

Persistent RV dysfunction is a critical factor determining the prognosis of PH patients. The strategies developed to treat/prevent RV dysfunction includes diuretics, atrial septostomy and mitral valve or right ventricle (MV or RV)-assist device, but emerging therapies targetting to reduce RV wall stress, including cardiac resynchronisation therapy, increasing myocardial oxygen delivery, and targetting mitochondrial metabolism, are still in the developing phase.[33]

It is critical to address the issue of delayed diagnosis and referral, as physicians often overlook symptoms, like fatigue and dizziness, in PH patients. As a result, patients may experience a significant delay in receiving appropriate care. The patients in the current study had an average symptom duration of 22.71±29.11 months before receiving specialised care. The REVEAL registry reported a two-year delay in PAH diagnosis from symptom onset, thus highlighting the importance of early referral to specialised PH care centres for better outcomes. Raising public awareness of PH, particularly among primary healthcare providers, is equally crucial, and can help avoid delayed diagnosis and treatment, which can lead to higher mortality rates. Furthermore, nearly three-fourths of PH patients reside in low-middle-income countries (LMICs) and experience several challenges, such as delayed diagnosis due to lack of awareness and delayed referral, limited access to expert personnel and specialised institutions, inadequate resources to afford care, and limited access to PH medications and surgical procedures, such as lung transplantation.[2,9,20,23]

The current study has limitations as only 25% of the participants had undergone RHC. Moreover, specific diagnostic tests, such as autoimmune workup, PFT, CPET and HRCT, were conducted in a limited number of patients based on their clinical context. Also, the study could not carry out ventilation-perfusion (V/Q) scans for CTEPH patients due to lack of resources.

Conclusion

The importance of early diagnosis and appropriate management of PH cannot be overemphasised. The NIPHeR could serve as a vital tool for understanding regional trends and guiding future clinical practice and research in PH.

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Non-Author Contributions

Aurangzaib Shaikh: Responsible for doing consultations in the pulmonary hypertension clinic and performing right heart catheterization.

Abdul Hakim Shaikh: Responsible for doing consultations in the pulmonary hypertension clinic and involved in all important decisions.

Ammara Rashid: Coordinating pulmonary hypertension clinics, managing patient data in Redcap, and maintaining patient follow-up.

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Abbreviations

NIPHeR: National Institute Pulmonary Hypertension Registry
NICVD: National Institute of Cardiovascular Disease, Karachi, Pakistan
NYHA FC: New York Heart Association Functional Class
ECG: Electrocardiography
RVH: (Right ventricle hypertrophy)
ERA: Endothelin receptor antagonist
PDE5I: Phosphodiesterase 5 inhibitors
mPAP: mean pulmonary artery pressure
RHC: Right Heart Catheterization
PAWP: pulmonary artery wedge pressure
WU: woods unit
PVR: pulmonary vascular resistance
IpcPH: Isolated postcapillary PH
CpcPH: combined postcapillary and precapillary PH
mPAP/CO: mPAP to cardiac output slope
PAH: Pulmonary arterial hypertension
MLIRs: Middle- and low-income regions
HIRs: High-income regions
PROKERALA: Pulmonary Hypertension Registry Of Kerala
HIV: human immunodeficiency virus infection
LMICs: low- and middle-income countries
PAPUCO: Pan African Pulmonary Hypertension Cohort
BPHR: Brazilian Pulmonary Hypertension Registry
GAP: Global Alliance for Pulmonary Hypertension registry
6WSPH: 6th World Symposium on Pulmonary Hypertension
PPHN: persistent pulmonary hypertension
COPD: chronic obstructive pulmonary disease
ILD: interstitial lung disease
CTEPH: chronic thromboembolic pulmonary hypertension
ESRD: end-stage renal disease
RVF: right ventricle failure
P2: pulmonic component of second heart sound
S3: third heart sound
TR: Tricuspid regurgitation
PR: Pulmonary regurgitation
CXR: Chest X-ray
PASP or sPAP: pulmonary artery systolic pressures
TRV: tricuspid regurgitation velocity
LV: Left ventricle
LA: Left Atrium
RA: Right Atrium
RV: Right Ventricle
PA: Pulmonary artery
PCWP: Pulmonary Capillary wedge pressure
NO: Nitric oxide
IV: intravenous
CCB: Calcium channel blocker
CTPA: Computed tomography pulmonary angiogram
6MWT: 6-minute walk test
RAD: right axis deviation
RBBB: right bundle branch block
QT and QTc: QT interval and corrected QT interval
S1Q3T3: In ecg, S wave in lead 1, Q wave in lead 3 and inverted T wave in lead 3
PE: pulmonary embolism
NT-proBNP: N-terminal pro-B-type natriuretic peptide
MRI: magnetic resonance imaging
FDG-PET/CT: 18F-flourodeoxyglucose positron emission tomography-computed tomography
FDA: Food and Drug Administration
ETA: Endothelin receptor A antagonist
ETB: Endothelin receptor B antagonist
PHC: Pulmonary Hypertension Clinic
CI: confidence interval
ABG: arterial blood gas
CBC: complete blood count
UCE: urea, creatinine and electrolytes
CPET: cardiopulmonary exercise testing
PFT: pulmonary function test
HRCT: high-resolution contrast CT
CTPA: CT pulmonary angiogram
ICU: intensive care unit
MV: mechanical ventilation
IQR: interquartile range
ANOVA: one-way analysis of variance
BMI: body mass index
LTOT: long-term oxygen therapy
DVT: Deep vein thrombosis
SAUDIPH: Saudi Arabia pulmonary hypertension registry
RECOPILAR: Collaborative registry of pulmonary hypertension in Argentina
US REVEAL: The Registry to Evaluate Early and Long-term PAH Disease Management
SIMURG: the RegiStry on clInical outcoMe and sUrvival in pulmonaRy hypertension Groups
COMPERA-CHD: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
USPHSR: The United States Pulmonary Hypertension Scientific Registry
ASPIRE: Adalimumab Biosimilar Patient Registry
RESPHIRAR: Southern Brazil registry (RESPHIRAR study)
ESC: European Society of Cardiology
ERS: European Respiratory Society
HCQ: hydroxycholoroquine
MRA: mineralocorticoid receptor antagonist
MV: Mitral valve
V/Q: ventilation/perfusion
DRAP: Drug Regulatory Authority Pakistan(31)

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JA, ASS, MH, AA, UT & MSA: Collectively developed the study design, data analysis, interpretation, revision and final approval.