

Pulmonary hypertension in Saudi Arabia: A single center experience

Esam H. Alhamad, Joseph G. Cal, Hussam F. Alfaleh¹, Mostafa Q. Alshamiri¹, Ahmad A. AlBoukai², Suliman A. AlHomida³

Departments of
Medicine, ¹Cardiology,
²Radiology, and
³Pharmacy, College
of Medicine,
King Saud University,
Riyadh, Saudi Arabia

Address for correspondence:

Dr. Esam H. Alhamad,
Pulmonary Division,
Department of
Medicine (38),
P.O. Box 2925,
College of Medicine,
King Saud University,
Riyadh 11461,
Saudi Arabia.
E-mail: esamalhamad@
yahoo.com

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Abstract:

CONTEXT: Several international studies have described the epidemiology of pulmonary hypertension (PH). However, information about the incidence and prevalence of PH in Saudi Arabia is unknown.

AIMS: To report cases of PH and compare the demographic and clinical characteristics of PH due to various causes in a Saudi population.

METHODS: Newly diagnosed cases of PH [defined as mean pulmonary artery pressure ≥ 25 mmHg at right heart catheterization (RHC)] were prospectively collected at a single tertiary care hospital from January 2009 and June 2012. Detailed demographic and clinical data were collected at the time of diagnosis, along with hemodynamic parameters.

RESULTS: Of the total 264 patients who underwent RHC, 112 were identified as having PH. The mean age at diagnosis was 55.8 ± 15.8 years, and there was a female preponderance of 72.3%. About 88 (78.6%) of the PH patients were native Saudis and 24 (21.4%) had other origins. Twelve PH patients (10.7%) were classified in group 1 (pulmonary arterial hypertension), 7 (6.2%) in group 2 (PH due to left heart disease), 73 (65.2%) in group 3 (PH due to lung disease), 4 (3.6%) in group 4 (chronic thromboembolic PH), and 16 (14.3%) in group 5 (PH due to multifactorial mechanisms). PH associated with diastolic dysfunction was noted in 28.6% of group 2 patients, 31.5% of group 3 patients, and 25% of group 5 patients.

CONCLUSIONS: These results offer the first report of incident cases of PH across five groups in Saudi Arabia.

Key words:

Chronic thromboembolic pulmonary hypertension, interstitial lung disease, left heart disease, pulmonary arterial hypertension, sarcoidosis

Pulmonary hypertension (PH), which is defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at right heart catheterization (RHC), comprises a spectrum of diseases that are categorized into 5 groups: Group 1, pulmonary arterial hypertension (PAH); group 2, PH due to left heart disease (LHD); group 3, PH due to lung disease; group 4, chronic thromboembolic PH (CTEPH); and group 5, PH with unclear multifactorial mechanisms.^[1]

Echocardiography is a useful tool for screening patients with PH. However, because of variability in echocardiographic assessments and significant limitations that may lead to over- or underestimation of systolic pulmonary artery pressure, RHC is the gold standard for confirming the diagnosis of PH.^[2-4] When seeking to measure the magnitude of this problem, such as in the context of healthcare plans for disease prevention and management, epidemiological studies on PH should only be based on gold standard measurements of pulmonary artery pressure. For more than two decades, the National Institutes of Health (NIH) registry has collected data on the epidemiologies of the idiopathic, familial, and anorexigen-associated forms of PAH, providing important information on survival and prognostic

markers among these patients.^[5,6] In recent years, a number of registries across different countries have been implemented to describe the natural history of PH arising from various causes.^[7-15] Thanks to these registries, the worldwide awareness of PH has increased substantially.

The true burden of PH in Saudi Arabia remains unknown. In the present study, we described a prospectively collected cohort of patients newly diagnosed (incident cases) with PH based on RHC at a single tertiary care hospital in Saudi Arabia over 36 months.

Methods

The present work is a descriptive study of consecutive patients newly diagnosed with PH between January 2009 and June 2012. This study was approved by the Institutional Review Board/Ethics Committee of the College of Medicine, King Saud University, Riyadh, Saudi Arabia. All patients understood the procedures required to establish the diagnosis, and written informed consent was obtained from all participants. A standard form was used to collect clinical information, including symptoms,

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smoking history, medication use, environmental history, occupational history, family history, and physical findings. Detailed blood testing, echocardiography, pulmonary function tests (PFTs), 6-minute walk test (6MWT), polysomnography, isotope perfusion scanning, high-resolution computed tomography (HRCT), and computed tomography pulmonary angiography were all included in the systemic diagnostic evaluation when PH was suspected.

PFTs (PFT Masterscreen; Jaeger, Hoechberg, Germany) were performed using standard methodologies, they included spirometry, plethysmography, and measurement of the diffusion capacity of the lung for carbon monoxide (DL_{CO}).^[16-18] The 6MWT was conducted in accordance with ATS guidelines.^[19] Heart rate, blood pressure, oxygen saturation (SpO_2), and the Borg dyspnea index^[20] were recorded at the beginning and end of a 6-minute walk. At the end of the test, the total distance walked (in meters; 6MWD) was documented. The World Health Organization (WHO) functional class and data from the PFTs and 6MWT were obtained within 2 days of RHC. The remaining test results were obtained within 5 days, except for those of the polysomnography, which was performed within 2 months of RHC.

RHC ($n = 264$) was performed on resting patients using standard techniques^[21] in the following cases: When PH was suspected on clinical examination, when a marked reduction in the predicted diffusion capacity of the lung for carbon monoxide ($DL_{CO} < 40\%$) was noted, when oxygen desaturation $< 88\%$ was evident during the 6MWT, or when indicated by the results of chest radiography, computed tomography, and/or echocardiography. Vasoreactivity testing with intravenous adenosine (in accordance with the current guidelines for the diagnosis and treatment of PH^[4]) was used in group 1 patients; however, none had a positive test.

PH-specific treatments [phosphodiesterase-5 inhibitors (sildenafil), endothelin receptor antagonists (bosentan), and prostacyclin analog (nebulized iloprost)] were used alone

or in combination, as clinically indicated. In addition, anticoagulants, diuretics, and oxygen therapy were used in accordance with the guidelines for the diagnosis and treatment of PH.^[4]

Statistical analysis

Descriptive statistics (means, standard deviations, and percentages) were used to describe the quantitative and categorical study variables. One-way analysis of variance was used for continuous measures. Kruskal–Wallis tests were used for nonparametric data. Chi-square statistics and the Fisher's exact test were used for categorical data. Student's *t* test for independent samples was applied to compare mean values of continuous variables. A two-sided $P < 0.05$ was considered statistically significant. SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

A total of 264 consecutive patients underwent RHC for suspected PH, of which, 152 patients did not have PH, instead 107 of them were diagnosed with interstitial lung disease (ILD), 21 with sarcoidosis, 7 with connective tissue diseases (CTDs) without ILD, 4 with sleep disorders, 3 with pulmonary embolism, 3 with bronchiectasis, 2 with chronic obstructive pulmonary disease (COPD), 2 with heart disease, and 1 each with hemolytic anemia, human immunodeficiency virus infection, and pulmonary Langerhans cell histiocytosis. The cases of ILD without PH ($n = 107$) included 38 with idiopathic pulmonary fibrosis (IPF), 35 with CTD-associated usual interstitial pneumonia (UIP), 16 with nonspecific interstitial pneumonia (NSIP), 8 with chronic hypersensitivity pneumonitis, 5 with respiratory bronchiolitis (RB)-associated ILD, 4 with unclassified fibrosis, and 1 with lymphocytic interstitial pneumonia (LIP).

In addition, 112 patients were identified as having PH and were divided into five groups according to the current classification of PH^[1] [Figure 1]. Comparison of demographic characteristics, clinical characteristics, and hemodynamic data among the five groups at the time of diagnosis are shown in Table 1.

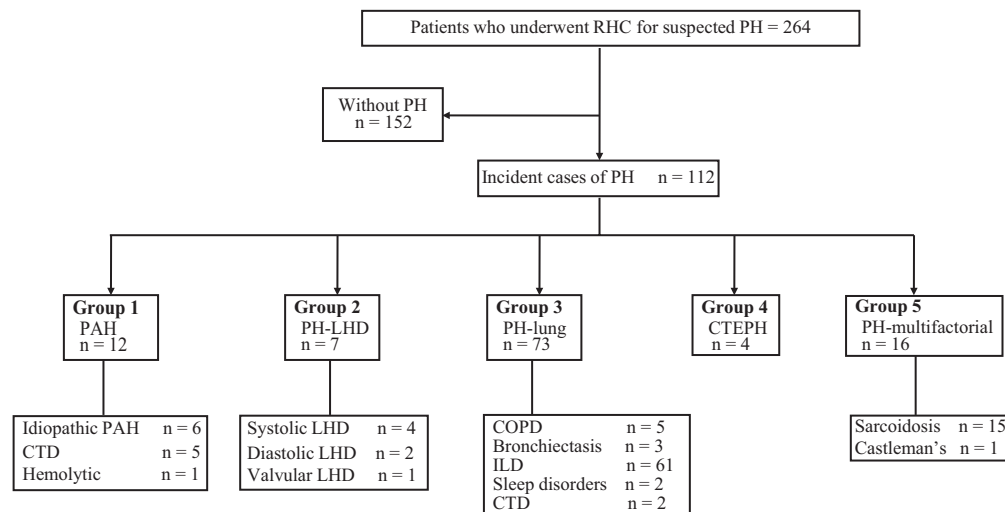


Figure 1: The study cohort [RHC, right heart catheterization; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; LHD, left heart disease; CTEPH, chronic thromboembolic pulmonary hypertension; CTD, connective tissue disease; COPD, chronic obstructive lung disease; and ILD, interstitial lung disease]

Table 1: Demographic and clinical characteristics among the five groups with pulmonary hypertension

Variables	Group 1 PAH n=12	Group 2 LHD n=7	Group 3 Lung n=73	Group 4 CTEPH n=4	Group 5 Multifactorial n=16	P value
Age, years	38.7±15.4	70.1±3.8	59.3±14.6	56.2±12.1	47.0±12.0	<0.0001
Female patients, n (%)	10 (83.3)	5 (71.4)	52 (71.2)	3 (75)	11 (68.7)	0.932
WHO FC: II/III/IV	1/11/0	1/6/0	34/36/3	2/2/0	6/7/3	0.039
Symptom duration, months	7.3±5.7	22.7±32.4	41.1±63.7	18.5±7.8	25.4±25.6	0.062
Ever smoker, n (%)	2 (16.7)	0	12 (16.7)	0	2 (11.8)	0.668
Baseline PFTs [†]						
FVC, %	77.0±15.5	56.2±9.2	56.8±21.0	68.4±17.0	60.3±17.2	0.025
FEV ₁ , %	74.8±15.5	59.2±10.4	62.2±22.4	69.4±10.8	60.4±17.7	0.130
FEV ₁ /FVC, ratio	83.5±5.3	87.2±9.9	89.6±10.2	86.4±9.6	84.6±12.5	0.043
TLC, %	78.4±17.6	72.5±20.7	60.5±18.2	63.2±7.9	66.5±19.2	0.041
DL _{CO} , %	59.6±16.2	75.5±48.1	37.1±20.9	62.1±9.8	41.6±15.7	0.001
Baseline 6MWT [‡]						
Distance, m	338.8±97.7	245.1±103.0	270.2±122.7	328.3±151.2	269.9±147.6	0.404
Initial SpO ₂ , %	98.0±1.9	96.4±2.8	94.9±3.2	95.0±0	93.5±4.1	0.003
Lowest SpO ₂ , %	90.0±7.0	91.0±6.6	85.8±7.9	89.7±1.2	84.5±7.5	0.131
Initial borg score	0.5±0.9	0.9±1.2	0.9±1.5	1.0±1.0	0.7±1.0	0.913
Final borg score	4.5±2.8	3.8±2.3	4.2±2.9	4.0±1.0	3.7±2.8	0.922
Echocardiography [§]	n=12	n=7	n=57	n=4	n=12	
SPAP, mm Hg	74.8±28.1	62.3±19.3	57.7±24.6	69.2±23.1	59.5±22.7	0.312
Hemodynamic data						
mPAP, mmHg	51.2±16.0	39.6±9.7	32.1±8.1	44.2±9.5	34.8±8.1	<0.0001
RAP, mmHg	11.1±4.2	10.7±1.6	6.9±3.9	11.8±6.8	7.5±5.1	0.002
sPAP, mmHg	76.8±26.5	59.6±16.1	48.4±13.9	71.0±22.1	51.2±13.7	<0.0001
PCWP, mmHg	11.0±2.6	21.0±7.7	13.3±5.8	14.5±11.6	13.2±6.3	0.079
PVR, Wood units	12.8±8.2	4.9±4.4	4.4±3.2	7.4±5.0	4.2±2.3	0.035
CO, L/min	4.3±2.9	4.3±1.1	5.1±1.5	4.4±1.2	5.6±1.4	0.046
Treatment, n (%) [§]						
Oral monotherapy	5 (41.7)	0	29 (39.7)	1 (25)	6 (37.5)	-
Oral combination	4 (33.3)	0	9 (12.3)	0	5 (31.3)	-
Prostacyclin combination	2 (16.7)	0	7 (9.6)	0	1 (6.3)	-

Data are presented as means±standard deviations or numbers (with percentages). Abbreviations: PAH = Pulmonary arterial hypertension; LHD = Left heart disease; CTEPH = Chronic thromboembolic pulmonary hypertension; WHO = World Health Organization; FC = Functional class; PFTs = Pulmonary function tests; FVC = Forced vital capacity; FEV₁ = Forced expiratory volume in one second; TLC = Total lung capacity; DLCO=diffusion capacity of lung for carbon monoxide; 6MWT = Six-minute walk test; SpO₂ = oxygen saturation by pulse oximetry; SPAP = systolic pulmonary artery pressure by echocardiography; mPAP = Mean pulmonary artery pressure; RAP = Right arterial pressure; sPAP = Systolic pulmonary artery pressure; PCWP = Pulmonary capillary wedge pressure; PVR = Pulmonary vascular resistance; and CO = Cardiac output, [†]One patient each from group 1, group 3, and group 4 could not perform the pulmonary function tests, and 1 patient in group 1, 13 patients in group 3, 1 patient in group 4, and 2 patients in group 5 could not perform the DL_{CO} test, [‡]One patient in group 1, 2 patients in group 3, and 1 in group 4 could not perform the 6MWT. [§]Two patients in group 1, 1 patient in group 2, 18 patients in group 3, and 3 patients in group 5 systolic pulmonary artery pressure could not be measured, [§]Including phosphodiesterase-5 inhibitors (sildenafil), endothelin receptor antagonists (bosentan), and prostacyclin analog (nebulized iloprost)

Overall, the mean age at diagnosis was 55.8 ± 15.8 years and there was a female preponderance of 72.3%. Eighty-eight (78.6%) of the patients were native Saudis and 24 (21.4%) had other origins (Yemen = 6, Pakistan = 6, Sudan = 4, Egypt = 4, and 1 each from Syria, Jordan, India, and Nigeria). More than half (55.4%) of the patients had severe symptoms at presentation (WHO functional class III). A total of 36.7% patients received oral monotherapy (sildenafil or bosentan), 16.1% received oral combination therapy, and 9% received a prostacyclin analog combination (nebulized iloprost with sildenafil and/or bosentan). At diagnosis, Doppler echocardiography was available for 92 of the 112 patients (82%) with PH (group 1 = 12, group 2 = 7, group 3 = 57, group 4 = 4, and group 5 = 12). However, systolic pulmonary artery pressure values can only be measured in 68 patients (group 1 = 10, group 2 = 6, group 3 = 39, group 4 = 4, and group 5 = 9).

In the PAH group (group 1), 6 patients were diagnosed with idiopathic PAH, 5 with CTDs [systemic lupus erythematosus (*n* = 3), polymyositis/dermatomyositis (*n* = 1), and undifferentiated CTD (*n* = 1)] and 1 with hemolytic anemia. Characteristically, these patients were younger and had shorter symptom durations than the other groups. Moreover, their hemodynamic data differed markedly from those of the other groups.

The patients with PH associated with LHD (group 2) included 4 patients with systolic dysfunction, 2 with diastolic dysfunction, and 1 with valvular disease. In comparison with the other groups, they were significantly older and had a markedly reduced walking distance. As was expected in this group, their pulmonary capillary wedge pressure (PCWP) was markedly elevated. Five patients have elevated transpulmonary gradient (TPG: mPAP-mPCWP) >15 mmHg.

Almost half (49.3%) of the patients with PH due to lung disease (group 3) presented with severe dyspnea (WHO functional class III). Their average symptom duration was 41 months, which was longer than that of any other group. As 83.6% of the patients in group 3 were diagnosed with ILD, it is not surprising that a restrictive ventilatory defect with a marked decrease in DL_{CO} was the predominant physiological pattern observed in this group. In addition, the walking distance was markedly reduced and significant oxygen desaturation was noted during the walking test. The ILDs observed in this group included 21 patients with IPF, 21 with CTD-associated UIP, 13 with NSIP, 4 with chronic hypersensitivity pneumonitis, and 1 each with LIP and RB-associated ILD. Post-capillary PH (defined as $mPAP \geq 25$ mmHg and $PCWP > 15$ mmHg) was noted in 23 patients (3 with COPD, 19 with ILDs, and 1 with sleep disorder). Forty-two patients with ILD were identified as having pre-capillary PH (defined as $mPAP \geq 25$ mmHg and $PCWP \leq 15$ mmHg). Comparisons of demographic and clinical characteristics among ILD patients with pre-capillary PH and those without PH are shown in Table 2. No difference in age, gender, functional class, or disease duration was noted between those with and without pre-capillary PH. However, ILD patients with pre-capillary PH showed significant reductions in DL_{CO} and walking distance as compared to those without PH. Sildenafil therapy was given to patients with IPF and chronic hypersensitivity pneumonitis, whereas sildenafil, bosentan, and nebulized iloprost were offered to patients with CTD-associated ILD, either as a monotherapy or in combination, as clinically indicated.

The patients with CTEPH (group 4) represented the smallest number of patients with PH. Their baseline PFTs, 6MWT, and hemodynamic data resembled those of group 1 patients [Table 1]. One patient was a candidate for pulmonary endarterectomy, but was lost to follow-up. Another patient had an operable distribution, but did not undergo surgery due to significant underlying comorbidities. The remaining two cases had inoperable CTEPH.

The cases of PH associated with multifactorial mechanisms (group 5) comprised 15 patients with sarcoidosis and 1 with Castleman's disease. Physiological impairments in the lung (i.e., restrictive ventilatory defects with decreases in DL_{CO}) were noted, but this was not unexpected given that all of our sarcoidosis patients had associated parenchymal lung involvements. Post-capillary PH was noted in 4 (26.7%) of the sarcoidosis patients (1 with stage II disease and 3 with stage IV, as assessed using the modified Scadding^[22] classification system). Comparisons of demographic and clinical characteristics among sarcoid patients with pre-capillary PH and those without PH are shown in Table 3. No between-group difference was observed in age, gender, or functional class. However, sarcoid patients with PH tended to have a longer duration of symptoms as compared to sarcoid patients without PH ($P = 0.07$). Stage IV disease was more frequent among patients with PH as compared to without PH. However, no significant difference was noted in the distribution of sarcoidosis stage among sarcoid patients with and without PH. The walking distance and oxygen saturation were markedly reduced among the sarcoid patients with PH as compared to non-PH patients.

Table 2: Comparison of demographic and clinical characteristics among interstitial lung disease patients with pre-capillary pulmonary hypertension and those without pulmonary hypertension

Variables	Without PH* n=102	With PH* n=42	P value
Age, years	57.8±14.1	59.4±15.4	0.435
Female patients, n (%)	61 (59.8)	30 (71.4)	0.254
WHO FC: II/III/IV	54/46/2	23/18/1	0.962
Symptom duration, months	36.2±37.6	39.4±56.6	0.933
Ever smoker, n (%)	25 (24.5)	9 (21.4)	0.830
Baseline PFTs [†]			
FVC, %	64.4±18.7	59.3±20.5	0.143
FEV ₁ , %	69.8±18.8	64.5±21.7	0.077
FEV ₁ /FVC, ratio	88.9±9.2	89.8±6	0.431
TLC, %	64.8±19.2	59.0±16.0	0.080
DL_{CO} , %	45.4±7	36.8±19.2	0.014
Baseline 6MWT [‡]			
Distance, m	329.5±120.3	281.1±113.1	0.011
Initial SpO ₂ , %	96.1±2.8	95.0±3.4	0.078
Lowest SpO ₂ , %	87.8±6.3	85.3±8.1	0.132
Initial Borg score	0.9±1.6	0.9±1.5	0.998
Final Borg score	4.0±3.0	4.4±3.0	0.493
Hemodynamic data			
mPAP, mmHg	18.9±3.8	31.7±8.1	<0.0001
RAP, mmHg	4.4±3.0	6.2±3.3	0.002
sPAP, mmHg	29.8±5.9	47.6±14.7	<0.0001
PCWP, mmHg	7.9±3.0	10.0±3.4	0.001
PVR, Wood units	2.6±1.2	5.4±3.7	<0.0001
CO, L/min	4.9±1.1	4.7±1.2	0.326

Data are presented as means±standard deviations or numbers (with percentages). See the legend to Table 1 for an explanation of the abbreviations that are not listed below. Abbreviations: PH = Pulmonary hypertension, *Nineteen patients in the pre-capillary PH group and 5 patients in the without-PH group were not included because their PCWP was >15 mmHg, †One patient in the PH group could not perform the pulmonary function tests, and 7 patients in the without-PH group and 8 patients in the PH group could not perform the DL_{CO} test, ‡ Three patients in the without-PH group could not perform the 6MWT.

During the study period, 13 patients with PH died [2 in group 1 (CTD associated PAH), 9 in group 3, and 2 in group 5] and 24 patients were lost to follow-up (1 in group 1 (idiopathic PAH), 5 in group 2, 14 in group 3, 1 in group 4, and 3 in group 5). Survival analysis was not performed due to the small sample size and the low numbers of deaths in each group.

Discussion

The present study is the first to report incident cases of PH (diagnosed based on RHC) across five classification groups in a Saudi Arabian population. This study represents the experience of a single center, whereas the previously reported international registries^[7-15] are multicenter, and there are differences in the numbers of cases and study durations. Nonetheless, some important extrapolations can be made.

PAH is a rare disease comprising of a group of heterogeneous disorders that share similar pathological changes (vascular proliferation and remodeling of small pulmonary arteries)

Table 3: Comparison of demographic and clinical characteristics among sarcoid patients with pre-capillary pulmonary hypertension and those without pulmonary hypertension

Variables	Without PH n=21	With PH* n=11	P value
Age, years	48.7±13.2	47.8±1	0.619
Female patients, n (%)	12 (57.1)	9 (81.8)	0.163
WHO FC: II/III/IV	9/12/0	7/3/1	0.142
Symptom duration, months	25.0±60.4	29.3±26.7	0.070
Ever smoker, n (%)	5 (23.8)	0 (0)	0.078
Sarcoidosis stage: II/III/IV	16/1/4	5/0/6	0.107
Baseline PFTs†			
FVC, %	71.6±13.7	67.5±15.1	0.606
FEV ₁ , %	70.8±13.2	67.1±14.6	0.351
FEV ₁ /FVC, ratio	82.5±7.9	84.9±10.0	0.204
TLC, %	74.0±18.0	66.9±19.4	0.137
DL _{CO} , %	47.6±18.4	42.6±15.1	0.333
Baseline 6MWT			
Distance, m	408.4±107.8	313.4±112.7	0.028
Initial SpO ₂ , %	96.6±2.1	93.4±4.1	0.013
Lowest SpO ₂ , %	87.7±13.3	85.6±8.0	0.142
Initial Borg score	1.2±1.8	0.4±0.5	0.546
Final Borg score	3.5±2.6	3.4±2.6	0.857
Hemodynamic data			
mPAP, mmHg	19.4±3.7	34.1±5.1	<0.0001
RAP, mmHg	4.6±2.8	6.0±4.1	0.359
sPAP, mmHg	28.9±5.4	49.9±9.4	<0.0001
PCWP, mmHg	7.7±3.9	9.6±3.6	0.120
PVR, Wood units	2.5±0.7	4.8±2.5	0.002
CO, L/min	4.9±1.2	5.8±1.5	0.128

Data are presented as means±standard deviations or numbers (with percentages). See the legends to Tables 1 and 2 for an explanation of the abbreviations. *Four patients in the pre-capillary PH group were not included because their PCWP was >15 mmHg. †One patient each in the with- and without-PH groups could not perform the DL_{CO} test.

and result in progressive dyspnea, right ventricular failure, and death.^[1,23,24] Worldwide, up to 70% of group 1 PAH cases have been attributed to idiopathic and PAH-associated CTD.^[7,10,14,15] In the present study, although group 1 contained a relatively small number of cases, almost all of them were related to idiopathic and PAH-associated CTD. Moreover, in agreement with the other registries,^[7,8,10] our PAH patients were predominantly women, younger, and showed severe functional classes at presentation. Interestingly, the interval between symptom onset and diagnosis among the PAH patients in our study (average, 7 months) was markedly shorter compared to that in the other registries (average, 24 months).^[7,10,11] One possible explanation for this is that our patients lacked the factors that reportedly contribute to delayed diagnosis recognition, such as symptom onset < 36 years of age, history of obstructive airways disease, sleep apnea, walking distance < 250 meters, mean right atrial pressure < 10 mmHg, or pulmonary vascular resistance (PVR) < 10 Wood units.^[25] Sex, race/ethnicity, and geographic region were not associated with delayed PAH recognition.^[25] During the study period, 2 of the PAH-associated CTD patients died; due to the limited number of patients, however, survival analysis could not be performed.

PH due to LHD (group 2) is one of the most common causes of PH. It can be caused by left ventricular (LV) systolic or diastolic dysfunction, or by valvular disease (predominantly mitral valve disorders). Echocardiographic identification of patients with an LV ejection fraction (EF) < 50% or left-sided valvular disease as a cause of PH is usually straightforward. However, a subgroup of patients with diastolic heart failure may present with progressive dyspnea, peripheral edema, and pulmonary congestion, and the ejection fraction obtained by echocardiography is well preserved in these patients.^[26] This frequently occurs in older patients with comorbidities, such as obesity, hypertension, diabetes mellitus, atrial fibrillation, and/or coronary artery disease.^[27,28] Such patients may require invasive testing, including RHC and/or left heart catheterization; these can provide measurements of PCWP, PVR, and LV end-diastolic pressure, particularly when the pretest probability of heart failure with preserved ejection fraction is intermediate.^[4,29] Other reports have indicated that an elevated TPG (>12 mmHg) suggests intrinsic changes in pulmonary circulation that are termed as “reactive PH.”^[4] In the present study, 71% of our PH-LHD patients were found to have elevated TPG > 15 mmHg, PCWP > 15 mmHg, and PVR > 3 Wood units, suggesting a mixed pattern of pre-capillary PH with diastolic dysfunction. Presently, there is no established treatment protocol for group 2 PH. Thus, large-scale studies are needed to determine the best therapeutic modality to prevent the development or progression of pulmonary vascular disease, hopefully leading to improvements in the quality of life and survival rate among PH-LHD patients.

In the present study, the largest cohort of PH patients distributed to group 3 (PH-lung). Notably, our center devotes significant time and resources to the study of diffuse parenchymal lung disorders. Thus, our data are clearly skewed by the number of ILD cases (83.5%), and patients suffering from PH associated with other respiratory diseases may have been missed. ILD is a heterogeneous group of disorders with similar clinical, radiological, and physiological aberrations that diffusely affect the lung parenchyma. Although ILD comprises of more than 100 distinct entities, the majority of ILD cases come from idiopathic interstitial pneumonias, CTD-associated ILD, sarcoidosis, and hypersensitivity pneumonitis. However, because of the plethora of possible mechanisms, PH related to sarcoidosis falls into group 5 (the multifactorial category, see below).^[11] PH in the context of ILD is associated with significant morbidity and mortality. As such, it is essential that we understand the changes that occur in the pulmonary vascular structure and function, leading to PH via various forms of ILD. The pathogenesis of ILD-associated PH is complex; it may include vascular remodeling due to chronic hypoxia, fibrotic destruction of the pulmonary vasculature, inflammation, thrombotic angiopathy, oxidant-antioxidant imbalance, cytokines, growth factors, and others.^[30,31] Diagnosing PH in the setting of ILD can be very challenging, as manifestations are subtle and commonly share similar symptoms until signs of right heart failure develop.^[30] This may explain why half of our group 3 patients presented with severe functional classes (III–IV). However, we do not know when the PH developed in our patients, as ILD and PH were simultaneously diagnosed in the same setting. This could explain why group 3 had the longest symptom durations as compared to the other groups. The baseline PFTs, 6MWT, and hemodynamic data

in group 3 resembled those of group 5, largely because the majority of group 5 patients were diagnosed with parenchymal sarcoidosis. When ILD patients with pre-capillary PH were compared to ILD patients without PH, no difference in age, gender distribution, functional class, or symptoms duration was noted. In the PH group, the DL_{CO} and the walking distance were significantly reduced as compared to those in patients without PH, but neither of these physiological variables was sensitive or specific enough to predict PH in the context of ILD.

Post-capillary PH was noted in 31.5% of the group 3 patients, two-third of whom had been diagnosed with ILD; this underscores the importance of detecting diastolic dysfunction as a possible cause of worsening dyspnea, particularly when there is no significant change in the physiological parameters that would suggest an alternative diagnosis. On the other hand, the presence of normal PCWP among ILD patients with pre-capillary PH does not necessarily exclude LV diastolic dysfunction. Exercise, volume challenge with saline, and vasodilation therapy has been suggested for the diagnosis of occult diastolic dysfunction in PH-LHD, but these options are limited by the lack of standardization and limited knowledge regarding abnormal responses to these tests.^[29,32] Thus, the value of these tests in the context of ILD is yet unclear, and future studies will be needed to explore the incidence of occult LV dysfunction and whether it has prognostic implications among ILD patients.

Despite the similarity in clinical manifestations and pathogenic mechanisms between PAH and PH associated with ILD, PH-specific therapy has not been shown to improve exercise capacity in IPF or systemic sclerosis patients with ILD complicated by PH.^[33,34] Nonetheless, there may be a subset of patients who could benefit from PH-targeting therapy, and future studies will be needed to determine that group of patients (if any) should be treated.

Information about the incidence and prevalence of CTEPH (group 4) is unknown. Recently, the Spanish registry reported an estimated incidence and prevalence of 0.9 and 3.2 cases per million adult inhabitants, respectively.^[10] In the present study, the CTEPH patients represented a minority group as compared to the others, either because they were substantially misdiagnosed or because they were not referred for consideration of pulmonary endarterectomy, which is the only curative treatment currently established for this group. The required surgical intervention is not available in our center, but in the absence of significant comorbidities, candidate patients are referred to other centers with considerable surgical experience. The potential benefit of treating CTEPH patients with PH-specific therapy has not been clearly established, but published studies suggest that these therapies may benefit inoperable patients and those with persistent PH after endarterectomy.^[35-38]

In group 5, multifactorial PH associated with sarcoidosis was the most common disease. The incidence and prevalence of PH in sarcoidosis patients has range of 5.7-73.8%, depending on the definition of PH, diagnostic methodology, patient ethnicity, institution, and world region.^[39-46] In the present study, the incidence of PH (both pre- and post-capillary) among patients newly diagnosed with sarcoidosis was 41.7%. Although PH associated with sarcoidosis commonly occurs in

advanced stage IV disease, previous study from this region^[46] as well as the present report, shows that sarcoidosis can occur even in stage II disease. Furthermore, apart from the marked reduction in walking distance noted in our sarcoidosis patients with PH, the other physiological variables failed to show any significant difference as compared to sarcoidosis patients without PH. Similar findings were noted in (group 3) ILD patients, emphasizing that the clinical suspicion of PH should be high particularly in the context of diffuse parenchymal lung disorders. Treatment of sarcoid patients with PH with PH-specific agents has not been clearly established, but retrospective analyses and small case series^[47-50] have suggested that there may be potential benefits in some patients. Future studies will be needed to determine that sarcoidosis patients would be most likely to respond to these agents.

In conclusion, we herein described a cohort of patients diagnosed with PH based on RHC at a single center in Saudi Arabia. The small size of the study population limited the study and prevented us from determining survival rates for the different groups of PH. However, we hope that the present data will improve awareness of this devastating condition and potentially motivate other centers to actively participate in a multicenter national registry.

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