Original Article

Pulmonary arterial hypertension in Saudi Arabia: Patients' clinical and physiological characteristics and hemodynamic parameters. A single center experience

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Abstract:

AIMS: The main objective of this study is to describe patients' clinical characteristics and physiological and hemodynamic parameters at the time of diagnosis in a pulmonary hypertension center in Saudi Arabia.

MATERIALS AND METHODS: This study reports the results from a single pulmonary hypertension specialized center in Riyadh, Saudi Arabia, namely Prince Sultan Medical Military City/Cardiac Center (PSMMC & CC). Both newly diagnosed (incidence) and referred (prevalence) cases of pulmonary arterial hypertension are included. All characteristics, including clinical, physiological, and hemodynamic parameters at the time of diagnosis are described.

RESULTS: A total of 107 patients were identified as having pulmonary arterial hypertension as diagnosed by right heart catheterization. The mean age at diagnosis was 36 (± 9) years, and there was a female preponderance of 62.6%. The mean duration between symptom onset and diagnosis was 27.8 (± 9.0) months. At the time of enrollment, 56.1% of patients were in functional class III and 16.8% were in functional class IV. Fifty five patients (51.4%) were diagnosed as idiopathic pulmonary arterial hypertension, 29 patients (27.1%) as congenital heart disease associated with pulmonary arterial hypertension, 16 patients (15.0%) as connective tissue diseases associated with pulmonary arterial hypertension, 4 patients (3.7%) as heritable pulmonary arterial hypertension, and 3 patients (2.8%) as portopulmonary hypertension.

CONCLUSION: This data highlights the current situation of pulmonary arterial hypertension in Saudi Arabia. Our patients are much younger than patients described in other international registries but still detected as late in the course of the disease. A majority of patients displays severe functional and hemodynamic compromise.

Key words:

Hemodynamics, pulmonary arterial hypertension, registry, Saudi Arabia, Saudi association for pulmonary hypertension, six minute walk test

Introduction

Pulmonary arterial hypertension (PAH) is characterized by progressive increase in pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP) that can lead to right heart failure and death.[1] The understanding of PAH pathobiology and the management of the disease have undergone significant advances during the last decade. Despite such improvement, PAH remains progressive and often fatal.

The National Institutes of Health (NIH) conducted the first registry of primary pulmonary hypertension (now known as idiopathic PAH [IPAH]) in the early 1980s.[2] Subsequently, a number of registries have been published to describe the natural history of PAH in different countries.[3-7] These registries have significantly improved our understanding on many aspects of PAH. The French registry of 674 adults with PAH has described the prevalence and incidence of the disease as well as the clinical and hemodynamic characteristics of IPAH patients.[3] Other surveys from America have focused mainly on the association between the environmental factors, particularly appetite suppressive drugs, and PAH.[8,9] A large prospective study (REVEAL Registry) in USA has described the characteristics of the demographics, clinical course, hemodynamic features, and disease management of PAH patients.[4]

The prognostic markers in PAH include a composite of measures that includes clinical

characteristics and physiological and hemodynamic parameters. The modified New York Heart Association (NYHA) functional class has been recognized as an important prognostic measure. Furthermore, exercise tolerance and biochemical and hemodynamic markers are also essential tools for categorizing PAH patients from both prognostic and therapeutic aspects.

The true burden of PAH in the Middle East and Saudi Arabia remains unknown, and the disease characteristics are yet to be determined. In the present study, we described the characteristics of PAH patients at the time of diagnosis in one center in Saudi Arabia.

Materials and Methods

The present study describes the results of prospectively collected and longitudinally followed cohort of patients diagnosed with PAH (both incidence and prevalence cases) in one tertiary specialized pulmonary hypertension (PH) center, Prince Sultan Medical Military City and Cardiac Center (PSMMC&CC), in Saudi Arabia over 3-year period.

Between December 2009 and November 2012, all patients referred to the pulmonary hypertension unit with suspected or confirmed diagnosis of WHO group I disease (PAH) were screened by using echocardiograph.

The diagnostic right heart catheterization (RHC) was necessary to meet the study inclusion criteria. RHC was performed in resting position using the Saudi Association for Pulmonary Hypertension (SAPH) RHC protocol. If appropriate wedging was not possible, left ventricular end-diastolic pressure (LVEDP) was directly measured.

The study protocol was reviewed and approved by the Registry and Research taskforces of the Saudi Association of Pulmonary Hypertension and by the Research and Ethics Committee of Prince Sultan Medical Military City.

Participants

Patients with newly diagnosed (incidence case) or previously diagnosed (prevalence case) PAH were eligible for enrollment if they fulfilled the definition of pulmonary hypertension (PH) group I PAH, as per the Nice 5th PH World Congress.[10] This includes patients with PAH that is idiopathic, heritable, or associated with congenital systemic-to-pulmonary shunts, connective tissue diseases, portal hypertension, drugs or toxins, HIV infection, or schistosomiasis.

The inclusion criteria were:

1. Age ≥ 14
2. PAH group 1 diseases (as described above)
3. Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest and pulmonary artery wedge pressure (PAWP) or LVEDP ≤ 15 mmHg, as measured by RHC.

Patients with splenectomy or hemoglobinopathies were excluded as this group has been moved from PAH group I diseases to PH group V diseases as per the Nice 5th PH World recommendation.

Data was collected using the SAPH-modified diagnostic and treatment protocol. The baseline assessment includes medical and drugs history, onset of symptoms, time of diagnosis, modified NYHA functional class at time of diagnosis, tests used to diagnose PAH that include pulmonary function test (PFT) including diffusion capacity, high resolution chest computerized tomography scan (HRCT), CT pulmonary angiography, V/Q scan, abdominal ultrasound, hepatic virology screen and liver function tests, immune screening, Schistosoma titer, and HIV serology. PHA group I disease category was also identified at this stage.

Physiological assessment at the time of diagnosis includes six-minute walk test (6MWT), NT pro BNP level, and echocardiographic evaluation for pericardial effusion and right ventricular function (TAPSE score).

RHC for hemodynamic parameters was performed in all patients (except 2) and included mPAP, right atrial pressure (RAP), cardiac index (CI), PAWP or LVEDP, and PVR. Only idiopathic and congenital heart diseases patients underwent vasoreactive testing using intravenous or inhaled Iloprost as per the protocol. The positive vasoreactive response is defined as a drop in mPAP by more than 10 mmHg to reach an absolute value of less than 40 mmHg in response to administration of acute vasodilator agent.

Statistical analysis

Descriptive statistics in terms of mean, standard deviations and percentages were used to describe characteristics of the studied patients. Comparison of categorical variables was conducted by Chi-Square test or Fisher's exact test accordingly. After assessment of normality distribution of variables, Student t-test and ANOVA test were used if data had normal distribution whilst Mann–Whitney and Kruskal–Wallis test were used in skewed data. A *P*-value less than 0.05 was considered a significant test. SPSS version 17 was used for all statistical analysis.

Results

A total of 128 patients with clinically suspected WHO group I PAH were evaluated. Of these, 107 patients (83.6%) met the study entry criteria and are described in this study [95 (89%) incidence cases and 12 (11%) prevalence cases]. Of those excluded, 2 patients had a normal RHC despite abnormal echocardiography (one patient had systemic sclerosis, SSc) and the other had pulmonary fibrosis with suspected "out of proportion" PAH); 4 patients had a high PAWP with normal transpulmonary gradient compatible with left-ventricular diastolic dysfunction; nine patients had WHO group IV chronic thromboembolic pulmonary hypertension (CTEPH); 3 patients had veno-occlusive disease (group I'), and 3 patients had WHO group III diseases. Figure 1 illustrates the distribution of the study population.

Demographics

The mean age at diagnosis was 36 (± 9) years. Out of the 107 patients, 67 (62.6%) were female. Three patients (2.8%) were non-Saudi in origin (1 Sudanese, 1 Jordanian, and 1 Yemeni). Eighty-four patients (78.5%) were geographically from the central province. Table 1 illustrates the demography of the patients enrolled in the study.

Table 1: Demography, clinical, and physiological characteristics of all patients

Variables	IPAH (*n* = 55)	HPAH (*n* = 4)	CHD-APAH (*n* = 29)	CTD-APAH (*n* = 16)	Po-APAH (*n* = 3)	*P* value
Age, year±SD	38±6	19±2	27±4	49±5	39±7	<0.001
Female, *n* (%)	36 (65.5%)	1 (25%)	18 (62.1%)	12 (75%)	0 (0%)	0.07
NYHA FC: II/III/IV	12/35/8	1/2/1	14/12/3	2/9/5	0/2/1	0.08
Symptoms duration, months	25.3±6.6	15.2±2.0	29.9±8.6	38.1±6.9	14.1±6.2	<0.001
Baseline 6MWT, meter	305±73	307±132	345±67	232±57	316±111	<0.001
Baseline NT-pro BNP	1274.9±735.9	2376.6±1936.2	980.4±744.5	2353.2±1583.4	1071.5±744.6	0.001
Echocardiography, TAPSE, mm	17.5±2.4	15.5±2.5	18.5±3.1	16.6±1.9	17.7±2.3	0.08

IPAH = Idiopathic pulmonary arterial hypertension, CHD-APAH = Congenital heart disease-associated pulmonary arterial hypertension, CTD-APAH = Connective tissue disease-associated pulmonary arterial hypertension, HPAH = Heritable pulmonary arterial hypertension, Po-APAH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension), NYHA = Modified New York Hear Association, 6 MWT = 6-minute walk test, TAPSE = Tricuspid annular plain systolic excursion

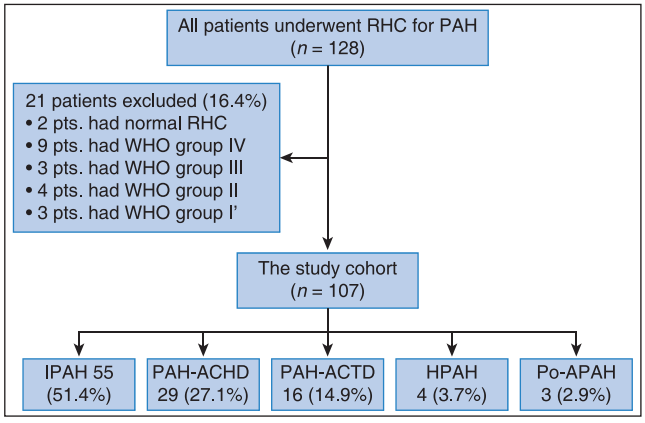

Figure 1: The distribution of the study cohort
RHC = Right heart catheterization, PAH = Pulmonary arterial hypertension, Pts., patients, WHO = World Health Organization, IPAH = Idiopathic pulmonary arterial hypertension, PAH-ACHD = Congenital heart disease-associated pulmonary arterial hypertension, PAH-ACTD = Connective tissue disease-associated pulmonary arterial hypertension, HPAH = Heritable pulmonary arterial hypertension, Po-APAH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension)

Baseline clinical characteristics

At the time of diagnosis, 29 patients (27.1%) were in modified NYHA functional class II, 60 patients (56.1%) were in functional class III, and 18 patients (16.8%) were in functional class IV. In the whole cohort of patients, the mean (± SE) time from symptoms onset to diagnosis was 27.8 (± 9.0) months. Fifty-five patients (51.4%) were diagnosed as IPAH, 29 patients (27.1%) as PAH associated with congenital heart disease (PAH-ACHD), 16 patients (14.9%) as PAH associated with connective tissue disease (PAH-ACTD) [systemic sclerosis (*n* = 11), mixed connective tissue disease (*n* = 4), systemic lupus erythematosus (*n* = 1)], 4 patients (3.7%) as heritable pulmonary arterial hypertension (HPAH) [based on strong family history but genetic testing was not performed], and 3 patients (2.9%) as portopulmonary hypertension (PoPH) [all with hepatitis B virus and portal hypertension]. The HPAH subgroup patients were younger than the other subgroups (mean age 19 (± 2) years), while the PAH-ACTD patients subgroup were the eldest (mean age 49 (± 5) years) and had more severe symptoms at diagnosis. Table 1 illustrates the baseline characteristics of the patients enrolled in the study.

Physiological and hemodynamics characteristics

The results of the physiological characteristics are shown in Table 1. Exercise capacity had been evaluated at the time of diagnosis in 104 patients (97.1%) by 6MWT. Cardiopulmonary exercise test was not performed in any patient. Echocardiograph results were available for all patients (100%) at the time of diagnosis. Systolic pulmonary arterial pressure estimation, TAPSE scoring, presence of pericardial effusion, and evaluation of diastolic and systolic function of the left ventricle were included in echocardiographic evaluation. Blood NT-pro BNP level was available in 80 patients (74.8%) at the time of diagnosis.

Diagnostic RHC was available in 105 patients (98.1%) at the time of diagnosis. Two patients were diagnosed as a very complex PAH-ACHD (complex single ventricle physiology with Eisenmenger), and both had previous cardiac cath done by their congenital heart disease specialist. The treating physician considered repeat RHC unnecessary and probably risky, and so the evaluation was made by echocardiography only.

The results of hemodynamics measurement are shown in Table 2.

Acute vasodilator challenge was performed in all 55 IPAH patients (100%) and in 17 patients (58.6%) of those diagnosed with PAH-ACHD. As per SAPH protocol, PAH-ACTD, HPAH, and PoPH patients were not tested for vasodilator challenge. Intravenous prostacyclin was used as the testing agent in 48 patients (66.5%), while inhaled Iloprost was used in 14 patients (19.4%) and IV adenosine in 10 patients (14.1%). The rate of positive acute vasodilator response was overall low and reported in 5 patients (6.9%) only.

Incidence versus prevalence cases

Incident cases were those newly diagnosed patients for whom diagnosis was first made during the recruitment phase of the study, while prevalent cases were those patients with a known diagnosis of PAH and referred to our center for further management.

Ninety-five (89%) incidence cases were diagnosed during the recruitment period, while 12 (11%) cases were referred to our center with an established diagnosis of PAH (prevalent cases). All prevalence cases had a repeat RHC at enrollment for complete hemodynamic study and confirmation of the diagnosis. Clinical and hemodynamic data for incident versus prevalent cases are shown in Table 3.

Finally, the correlation between the modified NYHA functional class and both physiological and hemodynamic parameters at the time of diagnosis is illustrated in Table 4.

Table 2: Hemodynamic measurements of all patients

Variables	IPAH	HPAH	CHD-APAH	CTD-APAH	Po-APAH	*P* value
mPAP, mmHg	54±10	55±8	52±8	41±6	49±9	<0.001
RAP, mmHg	13±3	13±3	9±3	9±1	10±2	<0.001
PAWP/LVEDP, mmHg	8±1	9±1	10±1	12±1	11±2	<0.001
PVR, Wood unit	19±6	22±8	14±6	11±4	13±5	<0.001
CI, L/min/m^2	2.2±0.6	1.9±0.7	2.8±0.7	2.4±0.7	2.7±0.8	0.001
Vasoreactivity, *n* (%)	4 (7.3%)^	ND	1 (3.4%)+	ND	ND	0.79

^Done in all IPAH patients, +Done in 17/29 CHD-APAH patients, IPAH = Idiopathic pulmonary arterial hypertension, CHD-APAH = Congenital heart disease-associated pulmonary arterial hypertension, CTD-APAH = Connective tissue disease-associated pulmonary arterial hypertension, HPAH = Heritable pulmonary arterial hypertension, Po-APAH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension), NYHA = Modified New York Hear Association, 6 MWT = 6-minute walk test, TAPSE = Tricuspid annular plain systolic excursion, mPAP = Mean pulmonary artery pressure, RAP = Right atrial pressure, PAWP = Pulmonary arterial wedge pressure, LVEDP = Left ventricular end diastolic pressure, PVR = Pulmonary vascular resistance, CI = Cardiac index, ND = Not done

Table 3: Clinical and hemodynamic data for incidence versus prevalence cases

Variables	All cases (*n* = 107)	Incident cases (*n* = 95)	Prevalent cases (*n* = 12)	*P* value
Age, year (range)	36.5±9.7	36.5±9.7	36.5±9.9	0.9
Female (%)	67 (62.6%)	62 (65.3%)	5 (41.7%)	0.1
NYHA, II/III/IV	29/60/18	25/54/16	4/6/2	
(%)	(27.1%)/(56.1%)/(16.8%)	(26.3%)/(56.8%)/(16.8%)	(33.3%)/(50%)/(16.7%)	0.9
Symptoms duration/month	27.8±9.0	27.8±9.3	27.4±6.5	0.9
6 MWT, meter	306.7±79.7	305.6±78.3	315.2±92.9	0.7
NT-pro BNP	1405.7±1076.6	1394.2±1004.5	1486.2±1558.8	0.9
TAPSE	17.54±2.6	17.5±2.6	17.8±2.9	0.7
Hemodynamics				
mPAP, mmHg	51.8±10.3	51.9±10.4	50.9±9.7	0.7
RAP, mmHg	11.75±3.3	11.6±3.2	13.0±3.6	0.2
PAWP, mmHg	9.9±1.9	9.9±1.9	10.3±2.1	0.6
PVR, Wood unit	16.8±7.1	16.8±7.2	16.9±6.7	0.9
CI, L/min/m^2	2.4±0.7	2.4±0.7	2.3±0.7	0.8
Disease subtype				
IPAH, *n* (%)	55 (51.4 %)	48 (50.5%)	7 (58.3%)	
HPAH, *n* (%)	4 (3.7%)	4 (4.2%)	0 (0.0%)	0.9
CHD-APAH, *n* (%)	29 (27.1%)	26 (27.4%)	3 (25.0%)	
CTD-APAH, *n* (%)	16 (14.9%)	14 (14.7%)	2 (16.7%)	
Po-APAH, *n* (%)	3 (2.9%)	3 (3.2%)	0 (0%)	

IPAH = Idiopathic pulmonary arterial hypertension, CHD-APAH = Congenital heart disease-associated pulmonary arterial hypertension, CTD-APAH = Connective tissue disease-associated pulmonary arterial hypertension, HPAH = Heritable pulmonary arterial hypertension, Po-APAH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension), NYHA = Modified New York Hear Association, 6 MWT = 6-minute walk test, TAPSE = Tricuspid annular plain systolic excursion, mPAP = Mean pulmonary artery pressure, RAP = Right atrial pressure, PAWP = Pulmonary arterial wedge pressure, LVEDP = Left ventricular end diastolic pressure, PVR = Pulmonary vascular resistance, CI= Cardiac index, NT-pro BNP = N-terminal brain natriuretic peptide

Table 4: Physiological & hemodynamic parameters according to NYHA FC at the time of diagnosis

	NYHA FC II	NYHA FC III	NYHA FC IV	*P* value
Number	29	60	18	
Age, year	32.9±8.2	37.5±9.8	39.1±10.6	0.05
Female, %	18 (62.1%)	39 (65.0%)	10 (55.6%)	0.7
Symptoms duration, m	28.2±9.7	27.7±9.4	27.4±6.8	0.9
6MWT, m	400.9±38.0	294.4±44.1	193.8±23.5	<0.001
NT-pro BNP	264.6±205.9	1312.7±525.8	3052.3±1150.9	<0.001
TAPSE, mm	21.5±1.8	16.7±1.1	14.7±0.9	<0.001
RAP, mmHg	8.5±1.8	12.6±2.8	14.1±2.7	<0.001
mPAP, mmHg	41.5±5.7	52.3±8.3	60.8±9.1	<0.001
PVR, wood unit	8.8±1.9	18.5±4.8	24.3±6.8	<0.001
CI L/min/m^2	3.3±0.3	2.1±0.4	1.7±0.2	<0.001

NYHA = Modified New York Heart Association, FC = Functional class, 6MWT = Six minute walk test, NT-pro BNP = N-terminal pro brain natriuretic peptide, RAP = Right atrial pressure, mPAP = Mean pulmonary artery pressure, PVR = Pulmonary vascular resistance, CI = Cardiac index

Discussion

PAH is a disease characterized by progressive increase in PVR and PAP secondary to progressive narrowing of the pulmonary arteries lumen.[1] Such abnormality is caused in part by smooth muscle contraction secondary to the imbalance between the vasoconstrictive and vasodilator mediators produced by the injured endothelial cells. More importantly, vascular remodeling caused by abnormal proliferation of all layers of the pulmonary arteries combined with a state of apoptosis resistance have been recently recognized as the main cause behind the abnormal rise in PVR in PAH.[10-13]

The first recognizable work on pulmonary hypertension was in year 1981, when NIH created a national registry of 187 patients with "primary" pulmonary hypertension".[2,14] Such early effort has led to major advances in the understanding of this disease. More recently, it has been recognized that several

diseases or conditions could be associated with PAH. These diseases share similar clinical and pathobiological features with IPAH.[15] During the last PH World congress 2013 in Nice, the classification of PH group was updated and PAH continues to be categorized as Group I diseases. This group includes IPAH, HPAH, drug- and toxin-induced PAH, and PAH associated with CHD, CTD, HIV, portopulmonary, and schistosomiasis.[16]

The present study describes the characteristics of PAH in the largest population of patients in Saudi Arabia to date. The clinical characteristics used in this study was limited to the modified NYHA functional class since this clinical parameter was found to have prognostic significance both at baseline[17] and follow up.[18] The physiological characteristics included 6 MWT, NT-pro BNP biomarker level, and TAPSE scoring as measured by echocardiography. 6MWT is a straightforward, safe, and reproducible test, which measures the distance walked in 6 minutes. It has been found to have a prognostic measure in PAH patients.[18,19] Similarly, both NT-pro BNP and TAPSE scoring have also been found to carry prognostic values.[20,21] Finally, hemodynamic characteristics included both diagnostic (mPAP and PAWP) and prognostic (RAP, CI, PVR, and vasoreactivity) parameters.[22,23]

In the current study, 107 adult PAH patients (95 incident cases and 12 prevalent cases; Table 1) were included. The mean age of the whole cohort at the time of diagnosis was significantly lower than the mean age reported by other registries.[3,4,6,7] This can probably be explained by the young age of the Saudi Arabian population, as more than 50% of the whole Saudi population is younger than 20 years of age.

The mean duration between symptom onset and diagnosis was unacceptably long (27.8 ± 9.0 months). As a result, 72.8% of the patients were in functional class III or IV at presentation. This delayed diagnosis is consistent with similar findings reported in many studies.[3,4,6] Because baseline modified NYHA functional class is a well-recognized predictor of outcome in PAH patients, the long duration of symptoms before establishing the diagnosis indicates insufficient awareness about the disease in Saudi Arabia. Alhamad *et al*., have recently published a single-center experience in managing PH in Saudi Arabia.[24] In his cohort of 112 PH patients, only 12 (10.7%) belonged to group I PAH, and almost all of them were related to IPAH and PAH-ACTD. Of interest, the reported symptoms duration before establishing the diagnosis was significantly shorter (7.3 ± 5.7 months) in that cohort.

IPAH was the most common subtype of PAH in our study. This observation has been recognized by other international registries.[3,5,25] Our IPAH patients were predominantly female and significantly older than the HPAH and PAH-ACHD patients but younger than PAH-ACTD ($P < 0.001$ between the groups). Similar to other registries, the majority of patients were at functional class III or IV at the time of diagnosis [Table 1].

PAH-ACHD patients were the second most common PAH subgroup and had the best physiological parameters compared to other groups. The high prevalence of PAH-ACHD in this cohort probably reflects the current practice of late detection of CHD patients in Saudi Arabia and delayed surgical corrections. Despite a relatively long duration of symptoms, those patients were more likely to be in modified NYHA functional class II compared to other group, although this did not reach the statistically significant level ($P = 0.08$ between the groups). Nevertheless, PAH-ACHD patients showed a significantly better physiological profile when compared to other PAH groups.

SSc was the leading cause of PAH-ACTD in our cohort. In SSc, the occurrence of PAH has been reported in more than 10% of patients and is known to have a major negative impact on outcome and survival.[26,27] Currently, international guidelines recommend to screen all asymptomatic SSc patients on an annual basis.[28] Our PAH-ACTD patients were significantly older than the other groups ($P < 0.001$ between groups) and had the longest duration of symptoms before confirming the diagnosis ($P < 0.001$ between groups). This is presumably related to the presence of other comorbidities that might be associated with CTD and can also lead to pulmonary symptoms, such as interstitial lung disease, heart failure, or myopathy. Furthermore, PAH-ACTD patients had significantly more physiological limitation when compared to other PAH groups ($P < 0.001$).

HPAH patients were the youngest among the groups. Both HPAH and PoPH patients had the shortest symptoms duration before establishing the diagnosis compared to other groups ($P < 0.001$). This is presumably related to the lower threshold for making the diagnosis because of involvement of other family members, and because of the severity of the symptoms.

Finally, although schistosomiasis is prevalent in certain regions of Saudi Arabia, we could not identify a single PAH case related to this infectious process. This could be attributed to detection or referral bias.

Hemodynamically, the HPAH group showed the most severe profile ($P < 0.001$ for RAP and PVR; $P = 0.001$ for CI; Table 2). The aggressive nature and poor outcome of HPAH has been well-recognized.[29] Conversely, and despite the worse physiological presentation, the PAH-ACTD patients expressed the most relatively benign profile. This discrepancy between the physiological and hemodynamic profiles in PAH-ACTD has been reported by others.[23,30,31] Patients with IPAH expressed a middle range of severity in our cohort. The relatively *good* CI observed in PAH-ACHD and PoPH was relatively due to the milder nature of the disease in the former and to known high cardiac output status in chronic liver disease in the latter condition [Table 2]. In addition, our data represent that acute responders to vasodilator challenge occur only in a small minority of patients (5 patients, 6.9%; Table 2). Because calcium channel blocker therapy is only indicated in positive acute vasodilator patients, we confirm that this therapy should never be used as an empirical trial.[32,33] Furthermore, the vasoreactive patients tended to have more benign physiological and hemodynamic profiles when compared to non-vasoreactive patients (NYHA FC II/III/IV 80%/20%/0% vs. 25%:57%:18%; 6MWT 388 m vs. 293 m; TAPSE 19 mm vs. 17 mm; NT-proBNP 668 pmol/l vs. 1429 pmol/l; mPAP 47 mmHg vs. 51 mmHg; CI 2.9 L/m/m^2 vs. 2.3 L/m/m^2; and PVR 12 WU vs. 16 WU, respectively; $P < 0.01$).

Finally, there were no distinctive features between the incidence and the prevalence cases in regard to clinical, physiological, or hemodynamic parameters [Table 3]. This could in part be related to the small number of prevalence cases in this study but may also be related to the recent time of diagnosis in some prevalent cases, which put them in a similar category as the incident cases. Traditionally, it is believed that the incidence cases have a worse prognosis when compared with prevalence cases.[34] Prevalence and incidence of PAH in Saudi Arabia cannot be calculated based on this early study and will be determined once the data from other centers involved in Pulmonary Arterial Hypertension in Saudi Arabia (PATENTS) registry conducted by the Saudi Association of Pulmonary Hypertension (SAPH) becomes available.

In conclusion, this descriptive study confirmed many characteristics similarities between Saudi PAH patients and the international data. Our patients still present very late in the course of the disease, and the majority of them display severe physiological and hemodynamic compromise. Of note, our patients are much younger when compared to the international registries.

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