Original Article

Saudi experience in the management of pulmonary arterial hypertension; the outcome of PAH therapy with the exclusion of chronic parenteral prostacyclin

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Abstract:

AIMS: The purpose of this study is to present our center's experience in managing patients with pulmonary arterial hypertension (PAH). The main objective is to describe patients' management profile and treatment outcome.

METHODS: This study presents the results from a single pulmonary hypertension (PH) specialized center in Saudi Arabia. Both incidence and prevalence cases are included. We have previously reported the clinical and physiological characteristics at the time of diagnosis for this cohort of patients. In this study, we describe the clinical management and the outcome of therapy in the same cohort, who were prospectively followed for a mean of 22 months.

RESULTS: A total of 107 patients were identified as having PAH. At the time of enrollment, 56.1% of patients were in modified New York Heart Association functional class (NYHA FC) III and 16.8% were in IV. Phosphdiesterase-5 inhibitor was the most commonly used target therapy (82.2%) followed by endothelin receptors antagonist (74.4%). Only five patients (4.7%) were candidate to use calcium channel blockers. Seventy-nine patients (73.8 %) received a combination nonparenteral target therapy. Thirty-one patients (28.9%) died during the follow-up period. Modified NYHA FC III and IV patients, portopulmonary hypertension, heritable PAH, and PAH associated with connective tissue diseases had the highest mortality rate ($P < 0.001$).

CONCLUSION: Our patients are detected at advanced stage of the disease, and thus the mortality is still unacceptably high. Advanced functional class at presentation and certain disease subgroups are associated with increased mortality.

Key words:

Mortality, prostacyclin, pulmonary arterial hypertension, Saudi association for pulmonary hypertension, target therapy

Pulmonary arterial hypertension (PAH) is a disease characterized by progressive obliteration of the pulmonary arteries leading to progressive increase of the pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP). Such high afterload causes eventually right ventricular failure and death.[1]

After the publication of the National Institutes of Health (NIH) registry of "primary pulmonary hypertension (PH)" in the early 1980s,[2] a number of registries have been published to describe the natural history and the outcome of PAH.[3-6] These registries have significantly improved our understanding on many aspects of PAH, including the predictors of outcome.

The French National Registry enrolled 354 consecutive patients with idiopathic (IPAH), heritable (HPAH), and drug-associated PAH. The reported 1- and 3-year survival rates in this registry were 87 and 67%, respectively. Univariate analyses suggested that female gender, modified New York Heart Association functional (HYHA FC) class I or II, greater 6-minute walk distance, lower right atrial pressure, and higher cardiac output are associated with a better prognosis. The multivariate analysis, however, reduced this list to gender, 6-minute walk distance, and cardiac output at diagnosis.[3] Similarly, the US REVEAL Registry (the Registry to Evaluate Early and Long-Term PAH Disease Management) from 54 centers has also been published.[7] The 1- and 3-year survival rates from the time of PAH diagnosis were 85 and 68%, respectively. Similar to the French registry, female gender, NYHA FC, and 6-minute walk distance were predictive of outcome. Additional prognostic

variables identified in the REVEAL included age, PVR, right atrial pressure (RAP), renal insufficiency, brain natriuretic peptide, pericardial effusion, low diffusing capacity of the lung for carbon monoxide, and resting systolic blood pressure and heart rate.

We have recently reported the clinical, physiological, and hemodynamic characteristics of PAH patients in Saudi Arabia.[8] In this study, we describe the treatment outcome and the predictive of survival of the same cohort of the patients recruited over 3-year period.

Methods

The method was described in detail in our previous article.[8] The present study describes the management outcome results of prospectively collected, and longitudinally followed cohort of patients diagnosed with PAH (both incidence and prevalence cases) in a specialized PH center, Prince Sultan Military Medical City and Cardiac Center (PSMMC&CC), in Saudi Arabia over 3-year period.

All patients referred to PH unit with suspected or confirmed diagnosis of PAH between December 2009 and November 2012 were screened by echocardiograph. A right heart catheterization (RHC) was mandatory to confirm the diagnosis and to meet the study inclusion criteria. The RHC was performed following the Saudi Association for Pulmonary Hypertension (SAPH) RHC protocol. If appropriate wedging was not satisfactory, left ventricular end-diastolic pressure (LVEDP) was then directly measured.

The study protocol was approved by the Registry and Research taskforces of SAPH and by the Research and Ethics Committee of Prince Sultan Military Medical City.

Both incidence and prevalence cases were included. Incident cases were the 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 irrespective of the period since diagnosis.

The inclusion criteria for enrollment are

- Age ≥14 years
- PAH group I diseases. This includes IPAH, HPAH, or PAH associated with congenital systemic-to-pulmonary shunts (PAH-ACHD), connective tissue diseases (PAH-ACTD), portal hypertension (Po-PH), drugs or toxins, human immunodeficiency virus (HIV) infection, or schistosomiasis.
- Mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest and pulmonary artery wedge pressure (PAWP) or LVEDP ≤15 mmHg, as measured by RHC.

Data is collected using the SAPH-modified diagnostic and treatment protocol.

The follow-up parameters include modified NYHA FC, 6-minute walk test (6MWT), NT-pro BNP level, echocardiography for prognostic parameters (Tricuspid Annular Plane Systolic Excursion (TAPSE) score and pericardial effusion), and hemodynamics. PAH treatments, concomitant treatments, and outcomes are also reported.

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's *t*-test and analysis of variance (ANOVA) were used if data had a normal distribution, whilst Mann–Whitney and Kruskal–Wallis test were used in skewed data. Cox regression model was used to adjust for different covariates that can affect survival among the studied group. A *P*-value of 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 World Health Organization (WHO) group I PAH were enrolled. Of these, 107 patients (83.6%) met the study entry criteria and are described in this study. Patients were prospectively followed for a mean duration of 22 ± 15 months. The details for those who were excluded have been described in the previous study.[8] Demographics and baseline characteristics for the whole group are illustrated in Table 1.

Ninety-five (89%) incidence cases and 12 (11%) prevalence cases were enrolled. All of the prevalence cases had a repeat RHC at enrollment for confirmation of the diagnosis and for complete hemodynamic study. There was no significant difference between the two groups in respect to the baseline clinical, physiological, or hemodynamic variables[8] or the outcome.

The details of using of PAH-specific treatments and combination therapy among all patients are shown in Table 2 and the use according to the functional class is illustrated in Table 3.

Eighty-four patients used sildenafil and only one (1.1%) patient discontinued the drug because of sudden loss of visual acuity, which turned to be unrelated to the drug. Out of the 80 patients who used bosentan, six (7.5%) patients developed hepatic toxicity; four (5.0 %) of them were shifted to another drug (three to ambrisentan and one to sildenafil). Inhaled iloprost was used in a total of 37 patients. Nine (24.3%) patients discontinued the treatment with this drug and were shifted to alternate therapy (six compliance issue, two facial skin rash, and one headache). Intravenous (IV) epoprostenol (Flolan) was only used in 12 patients as a rescue measure for 21 ± 6 days in inpatient situation, as safety logistics for outpatient use of this drug in Saudi Arabia is not ideal. Seven of those patients (58.3%) were discharged on oral therapy or subcutaneous (SC) treprostinil in combination.

Anticoagulation was used in 46 (84%) IPAH patients. Five (10.8%) patients stopped the drug (two because of minor bleeding/bruising and three because of inadequate follow-up) and one (2%) died secondary to massive abdominal bleeding.

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

Variables	Whole cohort (*n* = 107)	IPAH (*n* = 55)	HPAH (*n* = 4)	CHD-APAH (*n* = 29)	CTD-APAH (*n* = 16)	Po-PH (*n* = 3)	*P*-value
Age, year±SD	36±8	38±6	19±2	27±4	49±5	39±7	<0.001
Female, *n* (%)	67 (62.6%)	36 (65.5%)	1 (25%)	18 (62.1%)	12 (75%)	0 (0%)	0.07
NYHA FC: II/III/IV	29/60/18	12/35/8	1/2/1	14/12/3	2/9/5	0/2/1	0.08
Symptoms duration, months	27.8±7.2	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	298±162	305±73	307±132	345±67	232±57	316±111	<0.001
Baseline NT-pro BNP, pg/ml	1,405.7±2,015	1,274.9±735.9	2,376.6±1,936.2	980.4±744.5	2353.2±1583.4	1071.5±744.6	0.001
Echocardiography, TAPSE, mm	17.5±3.2	17.5±2.4	15.5±2.5	18.5±3.1	16.6±1.9	17.7±2.3	0.08
mPAP, mmHg	51±11	54±10	55±8	52±8	41±6	49±9	<0.001
RAP, mmHg	11±3	13±3	13±3	9±3	9±1	10±2	<0.001
PAWP/LVEDP, mmHg	11±2	8±1	9±1	10±1	12±1	11±2	<0.001
PVR, Wood unit	16±7	19±6	22±8	14±6	11±4	13±5	<0.001
CI, L/min/m^2	2.4±0.5	2.2±0.6	1.9±0.7	2.8±0.7	2.4±0.7	2.7±0.8	0.001
Vasoreactivity, *n* (%)	5 (4.7%)	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 heart association, 6MWT = 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 2: PAH-specific treatments and combination therapy among all patients (*n* = 107)

Variable	ETRA (*n* = 80) (%)	PD-5 inh (*n* = 88) (%)	Oral prostacyclin (*n* = 2) (%)	IV epoprostenol^ (*n* = 12) (%)	Inhaled iloprost (*n* = 27) (%)	SQ Treprostinil (*n* = 3) (%)	CCBs (*n* = 5) (%)
Monotherapy (28 patients)	9 (32.1)	12 (42.9)	—	—	3 (10.7)	—	4 (14.3)
Combined with one oral therapy, *n* (%)	42 (52.5)	44 (50)	2 (100)	—	12 (32.4)	1 (33.3)	—
Combined with non-oral prostacyclin, *n* (%)	5 (6.2)	8 (9.1)	—	—	—	—	—
Triple combination, *n* (%)	24 (30.0)	24 (27.3)	—	12 (100)	22 (59.5)	2 (66.7)	1 (20)

IV = Intravenous, ETRA = Endothelin receptors antagonists (bosentan and ambrisentan), PD-5 inh = Posphodiesterase-5 inhibitors (sildenafil), Oral prostacyclin = Beraprost sodium, NYHA FC = Modified new york heart association functional class, SQ = Subcutaneous, CCB = Calcium channel blockers. ^IV epoprostenol was used only as a short-term rescue treatment

Table 3: Use of PAH-specific treatments and combination therapy according to the functional class (*n* = 107)

NYHA FC	ETRA (%)	PD-5 inh (%)	Oral prostacyclin (%)	IV epoprostenol^ (%)	Inhaled iloprost (%)	SQ remodulin (%)	CCBs (%)
NYHA FC II (*n*=29)	15 (51.7)	12 (41.3)	0 (0)	0 (0)	11 (37.9)	—	4 (13.7)
NYHA FC III (*n*=60)	47 (78.3)	58 (96.6)	2 (3.3)	0 (0)	10 (16.7)	1 (1.6)	1 (1.6)
NYHA FC IV (*n*=18)	18 (100)	18 (100)	0 (0)	12 (66.7)	16 (88.9)	2 (11.1)	0 (0)

^IV epoprostenol was uses only as a short-term rescue treatment. ETRA = Endothelin receptors antagonists (bosentan and ambrisentan), PD-5 inh = Posphodiesterase-5 inhibitors (sildenafil), Oral prostacyclin = Beraprost sodium, NYHA FC = Modified new york heart association functional class, SQ = Subcutaneous, CCB = Calcium channel blockers

Thirty-one patients (28.9%) died during the follow-up period. One- and 3-year survival was 72 and 57% in the whole cohort (n = 107), respectively [Figure 1]. The cause of death was attributed to progression of the disease in 23 patients, massive hemoptysis in two (presumably secondary to pulmonary artery rupture), massive abdominal bleeding in one (the patient was on SC tinzaparin (Innohip)), three patients had very poor compliance to treatment (all were ≤17-years-old), and two portopulmonary hypertension patients had unrelated death secondary to hepatic failure. However, six patients were in functional class IV at presentation and died within 4 months of presentation.

The distribution of death between the different disease subgroups, modified NYHA FC, and the physiological and hemodynamic parameters is illustrated in Table 4.

Discussion

Management of PAH has undergone a major evolution in the past decade. Targeted therapy has led to a significant improvement in patients' symptoms and quality of life, a slower rate of clinical deterioration, and a better survival.[9] A meta-analysis of 23 randomized controlled study of PAH patients treated by modern drug therapies for an average of

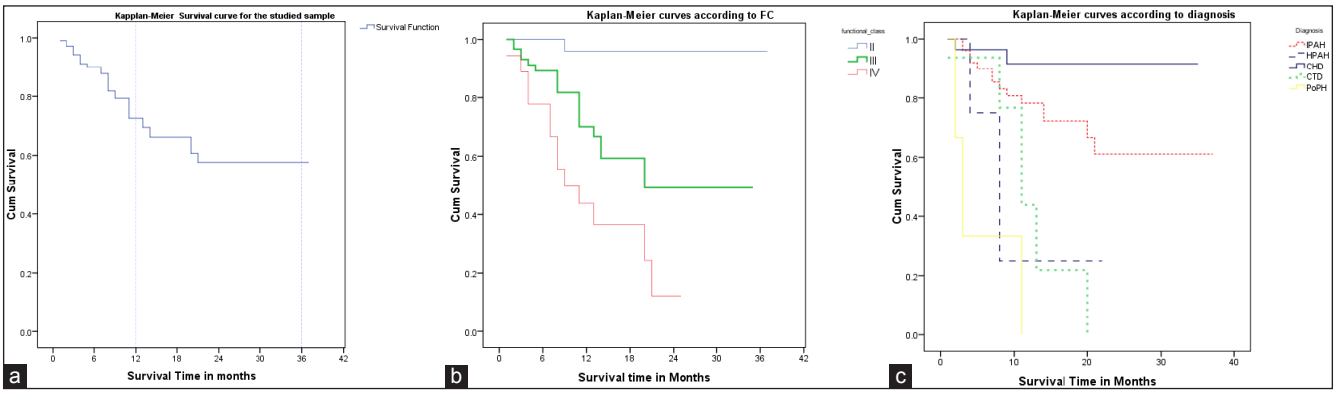

Figure 1: Overall survival and survival based on disease subtype and functional class. Overall survival in all cohorts (a), survival according to functional class (b), survival according to disease subtype (c). IPAH = Idiopathic pulmonary arterial hypertension, PAH-ACHD = Pulmonary arterial hypertension associated with congenital heart disease, PAH-ACTD = Pulmonary arterial hypertension associated with connective tissue disease, HPAH = Heritable pulmonary arterial hypertension, Po-PH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension)

Table 4: Distribution of death according to disease type, physiological, and hemodynamic parameters

Variable	Category (number of patients) (*n* = 107)	Number of death (% of total death) (*n* = 31)	(%) Of death within the class	*P*-value
Disease	IPAH (*n*=55)	14 (45.2)	25.5	<0.001
	HPAH (*n*=4)	3 (9.7)	75	
	PAH-ACHD (*n*=29)	2 (6.5)	6.9	
	PAH-ACTD (*n*=16)	9 (29.0)	56.2	
	Po-PH (*n*=3)	3 (9.6)	100	
NYHA FC	II (*n*=29)	1 (3.2)	3.4	<0.001
	III (*n*=60)	17 (54.9)	28.3	
	IV (*n*=18)	13 (41.9)	72.2	
Incidence/prevalence	Incidence (*n*=95)	27 (87.1)	28.4	0.7
	Prevalence (*n*=12)	4 (12.9)	33	
TAPSE	≥1.5 cm (*n*=99)	26 (83.9)	26.3	0.04
	<1.5 cm (*n*=8)	5 (16.1)	62.5	
6MWT	≥380 m (*n*=24)	2 (6.7)	8.3	0.01
	<380 m (*n*=80)	28 (93.3)	35	
NT-pro BNP	<1,500 pg/ml (*n*=52)	9 (33.3)	16.3	<0.001
	≥1,500 pg/ml (*N*=28)	18 (66.7)	64.3	
RAP	≤8 mmHg (*n*=19)	2 (6.5)	10.0	0.03
	>8 mmHg (*n*=86)	29 (93.5)	34.1	
CI	≥2.3 L/min/m^2 (*n*=41)	7 (22.6)	17.1	0.03
	<2.3 L/min/m^2 (*n*=64)	24 (77.4)	37.5	
mPAP	<45 mmHg (*n*=28)	7 (22.6)	23.3	0.4
	≥45 mmHg (*n*=77)	24 (77.4)	32	
PVR	<10 WU (*n*=27)	3 (9.7)	11.1	0.02
	≥10 WU (*n*=78)	28 (90.3)	35.9	

NYHA = Modified new york heart association, 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), TAPSE = Tricuspid annular plain systolic excursion, 6MWT = 6-minute walk test, NT pro BNP = *N*-terminal pro-brain natriuretic peptide, RAP = Right atrial pressure, CI = Cardiac index, mPAP = Mean pulmonary artery pressure, PVR = Pulmonary vascular resistance

14.4 weeks compared to placebo has shown a 43% reduction in mortality and a 61% reduction in hospitalizations.[10]

Many prognostic variables have been identified as treatment goal in the management of PAH. For instance, the modified NYHA functional classification has shown a clear prognostic predictive value in patients with PAH even when NYHA classification is assessed before or 3 months after the initiation of epoprostenol treatment.[2,11,12]

Similarly, biochemical markers such as NT-Pro BNP[13] and objective assessment of exercise tolerance in patients with PAH have been also found to be markers for disease severity[14,15] and to have prognostic significance.[16,17] Furthermore, echocardiographic indices that include the presence of a pericardial effusion, right atrial area index,[18-20] RV index (Tei index),[21,22] and TAPSE score[23,24] have also been reported to be useful prognostic measures. Finally, many hemodynamic parameters, such as RAP and

cardiac index (CI) have been found to have prognostic value.[25,26]

PH care started in Saudi Arabia in 2006 and matured significantly from 2009. Thus, it seemed timely to present our experience in managing this devastating disease and compare our results to international data.

In this study of 107 adult patients (95 "incident" and 12 "prevalent" cases), 55 patients were diagnosed as IPAH, four as HPAP, 29 as PAH-ACHD, 16 as PAH-ACTD, and three as Po-PH.

Of interest, unlike most international registries in which prevalent cases of PAH represented the majority of cases and corresponded to better outcome and survivors, in our series the majority of patients were incidence cases. This may reflect the poor awareness about the disease between the healthcare providers in Saudi Arabia and that most patients are detected late at tertiary care referral centers. More importantly and unlike most international series, there was no appreciable difference in the outcome between the incidence and prevalence cases in our series. However, the small number of the prevalent cases and the fact that most of them had short diagnosis duration putting them in a category similar to the incident cases make a real outcome comparison between these two groups very difficult.

Most of our patients presented late and were in advanced stage with poor prognostic variables. Furthermore, there was a significant association between disease subtype, NYHA FC, biomarkers, 6MWT, TAPSE score, and hemodynamic parameters, which include RAP, PVR, CI, and mortality [Table 4]. However, in multivariate analysis using Cox regression model to adjust for different covariates, only disease subtype and the modified functional classes were independent predictors of survival [Table 5]. Considering IPAH and modified NYHA FC II as the reference parameters, Po-PH patients had an increased mortality hazard of nearly five times and NYHA FC IV of about 28 times.

Until recently IV epoprostenol was the only treatment that had been shown to improve long-term survival in PAH patients. In two large series of patients treated with IV epoprostenol, 1-, 2-, and 3-year survival was 85 and 88%, 70 and 76%, and 63 and 63%, respectively.[11,12] Unfortunately the chronic use of IV epoprostenol is not a practical option in Saudi Arabia as patients might have difficulties getting urgent medical attention in case of pump failure or IV access complications. This has created a unique challenge to PH patients and PH specialists, and probably affected the prognostic outcome of some patients who were in need for such chronic therapy. Nevertheless, our data might be unique as it reports the outcome of largely nonparenteral prostacyclin-treated patients. In our series we used IV epoprostenol only as an inpatients' rescue measure for an average of 21 (±6) days in 12 patients, who presented in modified NYHA FC IV and signs of right ventricular failure. Seven patients were stabilized and eventually discharged home on combination therapy, while five patients died.

The concept of starting PAH treatment with a single oral agent followed by the addition of a second agent in case of an insufficient clinical outcome has been considered as the standard of care. Many registries have confirmed that combination treatment eventually became necessary in almost half of the patients, indicating that monotherapy may not provide sufficient efficacy in many PAH patients.[4-7] Nevertheless, favorable survival rates with first-line monotherapy (bosentan) have been reported in a study of 169 patients with IPAH, in which the survival rates at 1, 2, and 3 years were 96, 89, and 86%, respectively.[27]

In the present study 28 patients (26.2%) were treated by monotherapy; sildenafil was the most common used drug (12 patients, 42.8%) followed by endothelin receptors antagonist (nine patients, 32.2%) and inhaled iloprost (three patients, 10.7%). Five patients were vasoreactive and four of them received calcium channel blockers as monotherapy (14.3%).

Combination therapy was used in majority of patients (73.8%), reflecting the severe status of the disease in the majority of cases [Table 2]. The threshold for upfront combination or sequential triple combination therapy was low in order to compensate for the impracticality of the use of chronic IV epoprostenol therapy. Patients with PAH-ACTD and HPAH were routinely started on upfront combination therapy, while those who presented with two or more poor prognostic factors were eligible for rapid escalation for sequential triple therapy. Subcutaneous treprostinil was used in three patients in combination with oral therapy. Because of its relatively long half-life, this drug has a great potential for chronic usage in the future. Overall,

Table 5: Multivariate Cox regression model for different covariates that affect survival among the studied group using IPAH and NYHA FC II as references

Clinical parameters	Hazard ratio	95.% confidence interval for HR	
		Lower	Upper
NYHA FC II (*n*=29)	—	—	—
NYHA FC III (*n*=60)	8.1	1.0	67.1
NYHA FC IV (*n*=18)	28.2	3.4	232.8
IPAH (*n*=55)	—	—	—
HPAH (*n*=4)	3.9	1.0	15.5
PAH–ACHD (*n*=29)	0.2	0.2	1.4
PAH–ACTD (*n*=16)	1.3	0.5	3.6
Po–PH (*n*=3)	5.3	1.1	24.8
6MWT	0.9	0.9	1.0
TAPSE (mm)	1.5	0.8	2.5
NT–pro BNP	0.9	0.9	1.0
RAP	1.3	0.9	1.8
CI	1.1	0.7	16.8
PVRI	0.9	0.8	1.1

NYHA FC = Modified New York Heart Association functional class, IPAH = Idiopathic pulmonary arterial hypertension, PAH-ACHD = Pulmonary arterial hypertension associated with congenital heart disease, PAH-ACTD = Pulmonary arterial hypertension associated with connective tissue disease, HPAH = Heritable pulmonary arterial hypertension, Po-PH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension), 6MWT = 6-minute walk test, NT pro BNP = N-terminal pro brain natriuretic peptide, TAPSE = Tricuspid annual plain systolic excursion, RAP = Right atrial pressure, CI = Cardiac index, PVRI = Pulmonary vascular resistance index

84.6% of patients presented at modified NYHA FC III and 100% of patients presented at FC IV received combination therapy [Table 3].

Our 1- and 3-year survival is 72 and 57%, respectively [Figure 1]. This is comparable to the "high and very high risk" groups described in the REVEAL registry and the British registry, but relatively lower than other registries [Table 6].

Many reasons could explain this relatively lower survival results.

First, the impracticality of using chronic parenteral prostanoid therapy in Saudi Arabia has definitely affected the survival rate in some patients, especially those who presented with advanced, severe disease. Second, significant percentage of our patients presented at advanced stage with more than two risk factors and died within 1-3 months of presentation. In our cohort, those who presented at early modified NYHA FC II had excellent survival rate (1- and 3-year of 96 and 96%, respectively) compared to those presented at FC III (1- and 3- year survival rate of 70 and 48%, respectively) and FC IV (1- and 2- year survival of 43 and 12%, respectively) [Figure 1]. Third, most of our patients were incidence cases and so expected to have a worse prognosis when compared to other registries, where most patients were prevalent cases. In fact, the patients' population of the British registry, who were incidence cases and treatment naïve, had a similar outcome when compared to or results.[29]

Finally, the mortality in our cohort was clearly related to the disease subgroup, where PAH-ACHD patients had the most favorable prognosis, while HPAH and PAH-ACTD patients had the worse outcome [Figure 1]. Three patients presented with Po-PH and all died. Two of them died shortly (within 1 month) secondary to fulminant hepatic failure, while the third patient died secondary to RV failure. Physiological and hemodynamic parameters were also associated with poor outcome in a univariate modality [Figure 2].

In conclusion, the present study describes the largest population of patients with PAH in Saudi Arabia and is the first to report the clinical management, treatment outcome, and predictive of survival for a cohort of PAH patients in this country. Unfortunately, most patients are detected at advanced functional class, and thus the mortality is still unacceptably high. Specific disease subtypes, namely Po-PH, HPAH, and PAH-ACTD carry the worse outcome. Importantly, the outcome of this cohort describes a unique clinical situation of PAH treated patients of mostly incidence cases who are managed by nonparenteral therapy.

The SAPH has recently published the Saudi guidelines for the management of PH and has been conducting extensive awareness and educational programs that should hopefully

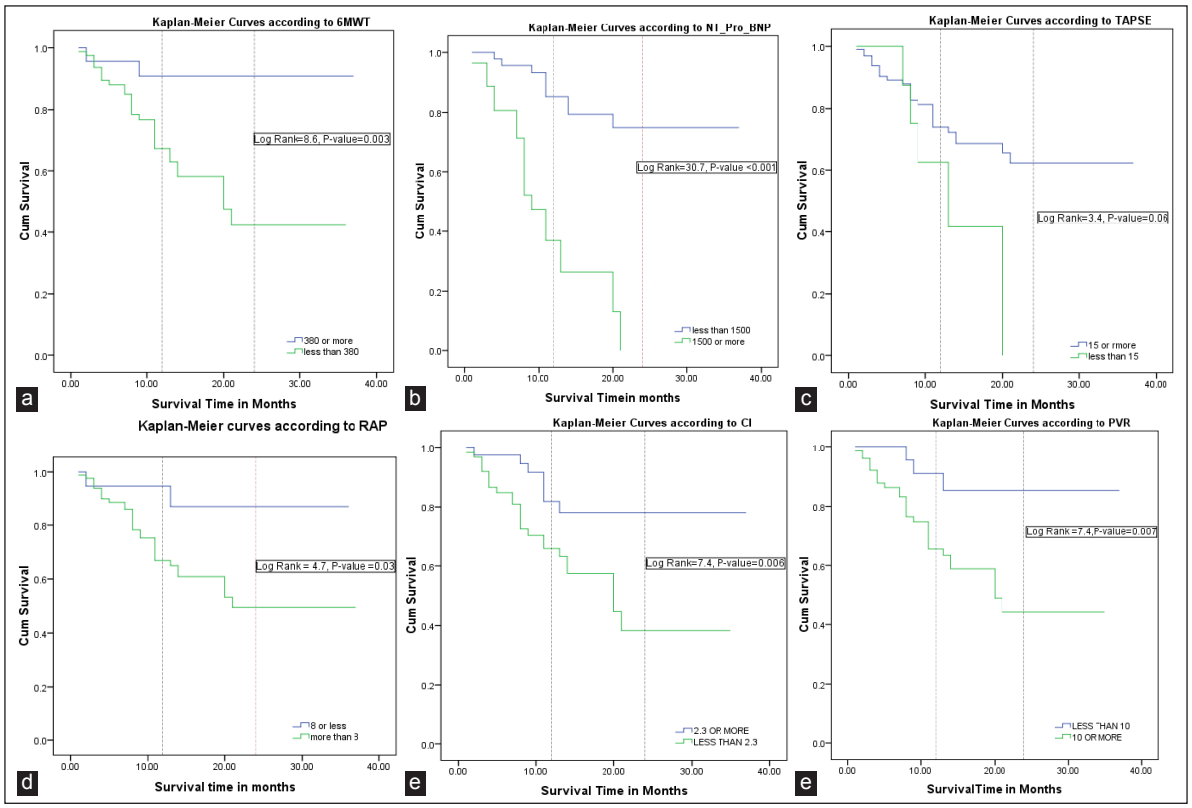

Figure 2: Association between physiological and hemodynamic parameters and survival. The association between survival and 6MWT (a), NT-pro BNP (b), TAPSE score (c), RAP (d), CI (e), and PVR (f) in univariate analysis. 6MWT = 6-minute walk test, NT-pro BNP = N-terminal pro brain natriuretic peptide, TAPSE = Tricuspid annual plain systolic excursion, RAP = Right atrial pressure, CI = Cardiac index, PVR = Pulmonary vascular resistance

Table 6: Survival of PAH based on different registries

Registry	Population and characteristics	Survival	
		Year	(%)
NIH[2]	IPAH	1	68
(*n*=194)	HPAH	3	48
(1981-1988)	Drug-APAH		
PH connection[28]	IPAH	1	84
(*n*=282)	HPAH	3	67
(1991-2007)	Drug-APAH		
French registry[3]	IPAH	1	87
(*n*=354)	HPAH	3	67.1
(2002-2003)	Drug-APAH		
REVEAL registry[7]	IPAH	1 (low risk)	> 95
(*n*=2716)	HPAH	1 (average risk)	90-95
(2006)	PAH-ACHD	1 (moderate risk)	85-90
	PAH-ACTD	1 (high risk)	70-85
	Po-PH	1 (very high risk)	<70
	HIV-APAH	3	68
	Drug-APAH		
Chinese registry[28]	IPAH	1	84.1
(*n*=90)	HPAH	3	70.6
(2006-2009)			
UK registry[29]	IPAH	1	79
(*n*=482)	HPAH	3	57
(2001-2009)	Drug-APAH		
PSMMC & CC	IPAH	1	72
(*n*=107)	HPAH	3	57
(2010-2012)	PAH-ACHD		
	PAH-ACTD		
	Po-PH		

IPAH = Idiopathic pulmonary arterial hypertension, PAH-ACHD = Pulmonary arterial hypertension associated with congenital heart disease, PAH-ACTD = Pulmonary arterial hypertension associated with connective tissue disease, HPAH = Heritable pulmonary arterial hypertension, Po-PH = Portal hypertension-associated pulmonary arterial hypertension (portopulmonary hypertension), HIV = Human immunodeficiency virus, NIH = National Institutes of Health, PH = Pulmonary Hypertension, PSMMC & CC = Prince sultan military medical city and cardiac center

further improve the outcome of PH patients in Saudi Arabia and helps in detecting patients at an earlier stages.[30]

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