Pulmonary hypertension experience in an expert university hospital

Ümit Yaşar Sinan, Rengin Demir, İsmail Polat Canbolat[1], Mert Palabıyık, Ayşem Kaya**, Mehmet Serdar Küçükoğlu*

Departments of Cardiology, *Cardiopulmonary Physiotherapy, **Biochemistry, İstanbul University Institute of Cardiology; İstanbul-*Turkey*
[1]Department of Cardiology, İstanbul Bilim University Şişli Florance Nightingale Hospital; İstanbul-*Turkey*

Abstract

Objective: Pulmonary artery hypertension (PAH) is characterized by remodeling of the small pulmonary arteries, leading to a progressive increase in pulmonary vascular resistance and right ventricular failure. In this study, we aimed to share our 10 years of experience dealing with pulmonary hypertension (PH) and provide information in real-life settings in terms of demographics, clinical course, PH subgroup distribution, and treatment patterns in patients with PAH in a tertiary center.

Methods: In this retrospective, single-center, observational study, we screened the patients who applied to PH outpatient clinic of İstanbul University Institute of Cardiology due to the suspicion of PAH between 2008 and 2017. While group 1, 4, and 5 PH patients were included, group 2 and 3 PH patients were excluded from the study.

Results: Our study group comprised 162 patients (115 females, 71%). The female:male ratio was 2.4. The mean age was 52±16 years. Most (86.4%) of the patients were in group 1 PH (PAH). The rest (13.6%, n=22) of the patients were in group 4 PH (chronic thromboembolic PH). In group 1 PH, 45.7% of patients (n=64) were classified as having idiopathic PAH (IPAH) after excluding the alternative diagnosis using PH diagnostic algorithm. The remaining 54.3% of group 1 PH patients (n=76) had various diseases that caused PAH, which is called associated PAH (APAH); APAH group included PAH associated with congenital heart diseases (n=70), connective tissue disorders (scleroderma, n=4) and portal hypertension (n=2).

Conclusion: Our data provides important information in real-life settings in terms of demographics, clinical course, PH subgroup distribution, and treatment patterns in patients with PAH in a reference tertiary center in Turkey. *(Anatol J Cardiol 2018; 20: 35-40)*

Keywords: pulmonary arterial hypertension, pulmonary vascular disease, chronic thromboembolic pulmonary hypertension, demographics, pulmonary arterial hypertension associated with congenital heart disease

Introduction

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary artery pressure (PAPm) ≥25 mm Hg at rest as assessed using right heart catheterization (RHC) (1). The term pulmonary artery hypertension (PAH) describes a disorder in a group of PH patients hemodynamically characterized by the presence of pre-capillary PH, which is defined by a PA wedge pressure ≤15 mm Hg and a pulmonary vascular resistance (PVR) >3 Wood units (WU) in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH (CTEPH), or other rare diseases (1). PAH is characterized by remodeling of the small pulmonary arteries, leading to a progressive in PVR and right ventricular (RV) failure (2).

The clinical classification of PH is intended to categorize multiple clinical conditions into five groups according to their similar clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategy as idiopathic or associated PAH (group 1), PH due to left heart disease (group 2), PH due to lung disease (group 3), CTEPH and other PA obstructions (group 4), and PH with unclear and/or multifactorial mechanisms (group 5) (1).

The true prevalence of PAH in the general population is unknown, likely because of its broad classification and multiple etiologies. In Europa PAH, prevalence and incidence are in the range of 15-60 subjects per million population and 5-10 cases per million per year, respectively (3, 4). Women are more susceptible to PAH than men (female:male ratio, 1.5-2.0). The PAH preva-

Address for correspondence: Dr. Ümit Yaşar Sinan, İstanbul Üniversitesi Kardiyoloji Enstitüsü, Kardiyoloji Anabilim Dalı, İstanbul-*Türkiye*
Phone: +90 533 396 84 03 Fax: +90 212 459 20 69 E-mail: drumityasar@hotmail.com
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lence in Turkey is unknown, but according to the PAH prevalence in Europa, we assume that there are 1500-4500 PAH patients in Turkey.

In this study, we aimed to share our 10 years of experience dealing with PH and provide information in real-life settings in terms of demographics, clinical course, PH subgroup distribution, and treatment patterns in patients with PAH in a tertiary center.

Methods

In this retrospective, single-center, observational study, we screened the patients who applied to PH Outpatient Clinic of İstanbul University Institute of Cardiology with the suspicion of PAH between 2008 and 2017. While group 1, 4, and 5 PH patients were included, group 2 and 3 PH patients were excluded from the study.

The patient's demographic characteristics and co-morbidities were recorded from their medical documents. Functional capacity, 6-min walking distance (6MWD), symptom status (rest dyspnea, syncope, etc.), right heart failure signs on physical examination, and N-terminal pro-B-type natriuretic peptides (NT pro-BNP) and uric acid levels were also recorded. Electrocardiograms (ECGs) of all patients were examined, and their heart rhythm was recorded. Transthoracic echocardiography (TTE) reports of all patients were reviewed and tricuspid annulus peak systolic excursion (TAPSE); pericardial effusion; RV ejection fraction (RVEF); and systolic, diastolic, and mean PAP were recorded. Vasoreactivity (VR) test results, right atrial pressure (RAP), PAPm (before and after VR test), PVR, and cardiac output were recorded from RHC reports. A positive vasodilator response was defined as a reduction in the mean PAP of >10 mm Hg, leading to a PAP of <40 mm Hg, with a normal or high cardiac output in VR test. Patient's medical therapies were classified as endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE-5is), prostacyclin analogs and prostacyclin receptor agonists, soluble guanylate cyclase stimulators, and calcium channel blockers (CCBs; for VR-positive patients). Patients were also classified according to their medical therapy as monotherapy and combination therapy groups.

Ethics Committee approval was obtained for the study protocol. Informed consent forms were signed by all patients.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 21.0 (IBM SPSS Statistics, IBM Corp., NY). All data were expressed as mean±SD or median (minimum-maximum) for continuous variables and as percentages for categorical variables. Kolmogorov-Smirnov test was used to identify distribution of variables normally. Student's t-test or Mann-Whitney U test was used to compare continuous variables, and x^2 test was used to compare categorical data. A p value of <0.05 was considered to be significant.

Results

Our study group comprised 162 patients (115 females, 71%). The female:male ratio was 2.4. The mean age was 52±16 years. Most (86.4%) of the patients were in group 1 PH (PAH). The rest (13.6%, n=22) of the patients were in group 4 PH (CTEPH) (Fig. 1a). There were no group 5 PH patients. In group 1 PH, 45.7% of patients (n=64) were classified as having idiopathic PAH (IPAH) after excluding the alternative diagnosis using PH diagnostic algorithm. None of these patients had undergone genetic tests for detection of mutations that cause PAH (such as mutations in bone morphogenetic protein receptor 2 or others) because we do not perform genetic testing at our hospital. The remaining 54.3% of group 1 PH patients (n=76) had various diseases that cause PAH, which is called associated PAH (APAH). APAH group included PAH associated with congenital heart diseases (CHD; PAH-CHD) (n=70), connective tissue disorders (scleroderma,

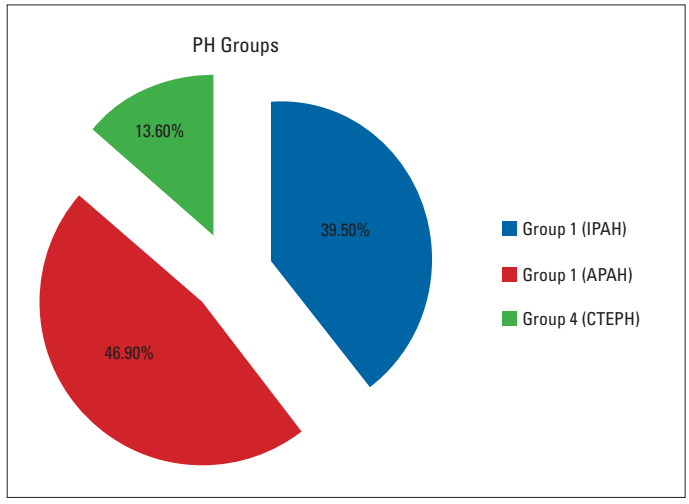

Figure 1. a. The distribution of pulmonary hypertension groups

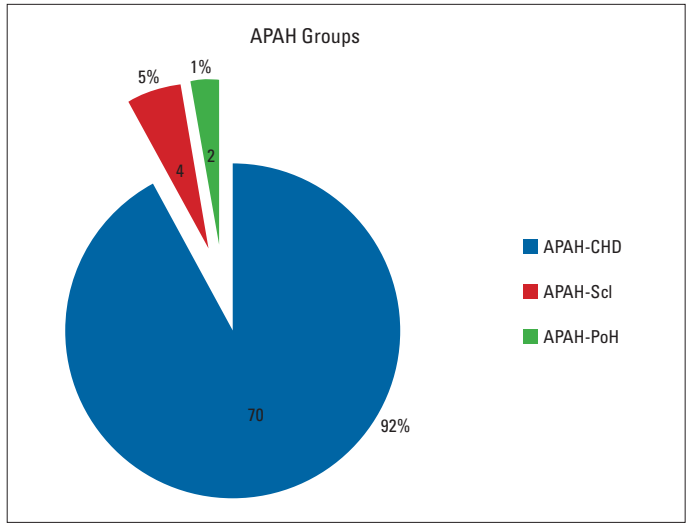

Figure 1. b. The distribution of associated pulmonary artery hypertension groups

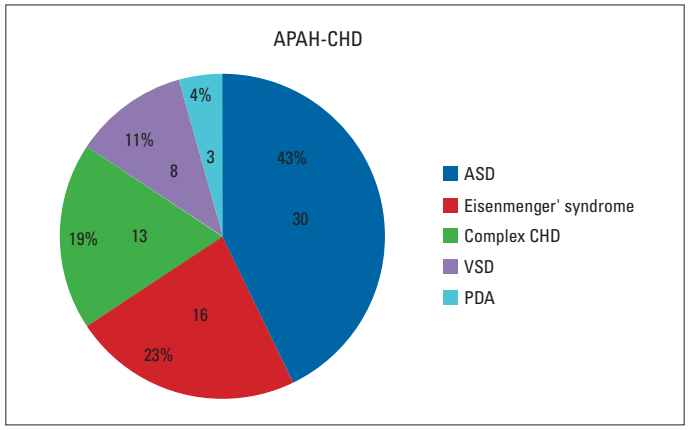

Figure 2. The distribution of pulmonary artery hypertension-congenital heart disease groups

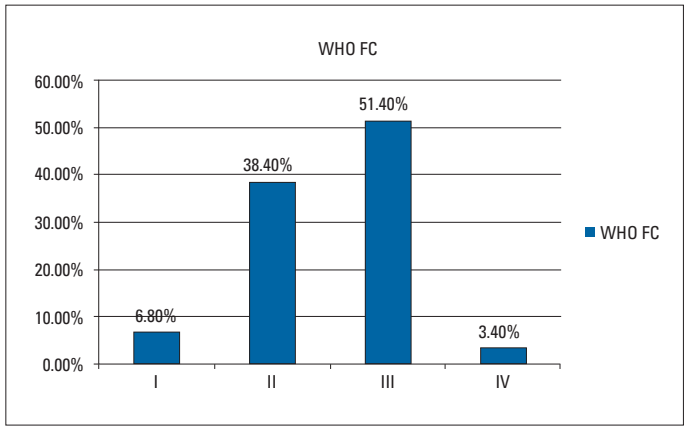

Figure 3. The distribution WHO FC of patient population

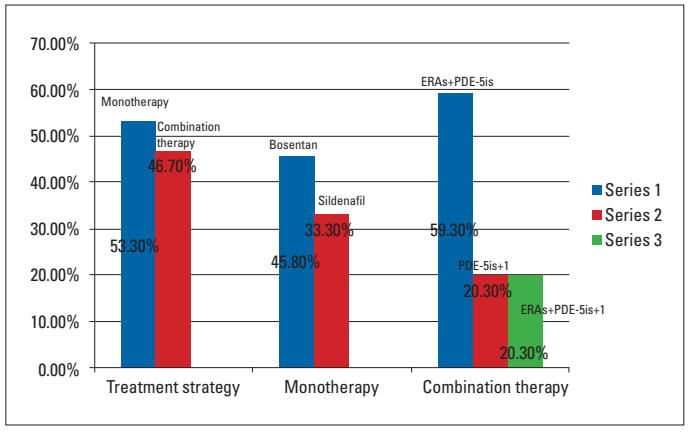

Figure 4. Treatment strategies

n=4), and with portal hypertension (n=2) (Fig. 1b). There were 30 patients with atrial septal defect (ASD) (closed or not closed), 16 with Eisenmenger syndrome, 13 with complex congenital heart disease, 8 with ventricular septal defect, and 3 with patent ductus arteriosus in PAH-CHD group (Fig. 2).

At the time of diagnosis, 6.8%, 38.4%, 51.4%, and 3.4% of all the patients with PH belonged to the World Health Organization (WHO) functional class (FC) I, II, III, and IV, respectively (Fig. 3).

Table 1. Characteristics of idiopathic pulmonary artery hypertension and pulmonary artery hypertension groups

n	IPAH (64)	APAH (76)	*P* value
Age (years)	76.6±25.8	93.0±33.4	<0.001
Female (%)	68.8	65.8	0.392
WHO FC II-III (%)	78.1	78.9	0.193
Mean sPAP (mm Hg)	76.6±25.8	93.0±33.4	0.004
TAPSE (mm)	18±4 mm	17±4 mm	0.392
Pericardial effusion (%)	1.5	1.3	0.951
CQ (mL/min)	4.1±1.4	4.6±2.0	0.267
Initial 6 MWT (m)	346	366	0.362

APAH - associated pulmonary artery hypertension; IPAH - idiopathic pulmonary artery hypertension; PAP - pulmonary artery pressure; TAPSE - tricuspid annulus peak systolic excursion

While the mean 6MWD at admission was 353.7±117 m, the median NT pro-BNP value was 760 pg/mL (min: 37 pg/mL, max: 20.564 pg/mL). On ECG, the rhythm was normal sinus rhythm in 82.7% of patients. Atrial fibrillation or flutter was the main rhythm in 17.3% of the patients. TTE revealed a PAPm of 75 mm Hg. On assessing RV function mean TAPSE was 17±5 mm and mean RVEF was 36.1±10.1%. Pericardial effusion was seen in 15.7% of patients on TTE. VR test with inhale ilioprost was positive in four patients on RHC. On RHC, PAPm before VR test was 58.1 mm Hg, and after VR test it was 55.4 mm Hg. PVR was 13.9 WU before VR and 10.4 WU after VR. Mean right atrial (RA) pressure was 16.5 mm Hg, and mean CQ was 4.3 L/min.

There were 50 females in APAH (n=76) and 44 females in IPAH (n=64) groups. Most of the patients belonged to WHO FC II and III in both the groups (50/64 in IPAH group and 60/76 in APAH group). The number of patients belonging to WHO FC IV was similar in both the groups (four patients in IPAH group and three patients in APAH group). Pericardial effusion was observed on TTE in nine patients in both the groups. The patients in IPAH group were much older than those in APAH group (57.0±15.7 years vs 46.4±15.2 years). On TTE, the mean sPAP was found to be higher in APAH patients (93.0±33.4 mm Hg) than in IPAH patients (76.6±25.8 mm Hg). Initial 6MWdiameter was higher in APAH patients (366 m) than in IPAH patients (346 m). RAP (15.8±6.5 mm Hg vs. 15.5±7.2 mm Hg) and CQ (4.1±1.4 L/ min vs. 4.6±2.0 L/min) were similar between IPAH and APAH patients; TAPSE was also similar between the two groups (18±4 mm vs. 17±4 mm) (Table 1).

Monotherapy was the preferred treatment strategy in 53.3% (n=72) of all the patients; 46.7% (n=64) patients were receiving combination therapy. Bosentan was the most preferred agent for monotherapy (45.8%; n=33). The second most preferred agent after bosentan was sildenafil (33.3%; n=24). ERAs and PDE-5is combination was the most preferred combination therapy (59.3%; n=38). Thirty of 38 patients were treated with sequential combination therapy, and upfront combination therapy was the initial treatment strategy in the remaining 8

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patients. PDE-5is +inhale ilioprost and triple combination with ERAs+PDE-5is +inhale ilioprost were the treatment strategy in 13 (20.3%) patients. Three patients were treated with parenteral therapy; two of them were taking triple combination therapy including i.v. epoprostenol+ERAs+PDE-5is and one was taking s.c. trepostinil+ERAs+PDE-5is combination. Four patients that showed positive VR test were taking high-dose CCBs. There were no differences between monotherapy and combination therapy groups regarding age, sex, PABm on RHC, and 6MWT improvement with treatment (or delta 6MWT) (Fig. 4).

Discussion

Over the past three decades, a number of PAH registries have reported information about the demographic, clinical, and hemodynamic characteristics of patients with PAH (5-16). In this study, we report our 10 years of experience dealing with PAH at a tertiary care university hospital in Turkey. The aim of our study was to provide information about patient's demographics, clinical courses, subgroup distributions, and treatment patterns at a reference PH center in the modern treatment era.

Recent data from various PAH registries indicate that the demographics of IPAH patients have changed. The mean age at diagnosis is increasing among PAH patients due to improvement in the diagnosis and treatment of PAH. The NIH registry reported a mean age ± SD at diagnosis of 36±15 years in IPAH patients (5). Contemporary registries report older populations ranging from 50±17 years to 65±15 years (6-9, 13-16). The Chinese registry has reported age at diagnosis and demographics similar to those reported in the US-NIH registry (11). The mean age of our study population was similar to that of study populations in a large-scale study from United States (US REVEAL) (6) and European registries (French registry) (7). Although the mean age of our patients was similar to that of those in the international registries, it was higher than that of those in the other Turkish registries. Registry on clinical outcome and survival in pulmonary hypertension groups (SIMURG) (17) was a nationwide PAH registry that was established by the Pulmonary Vascular Diseases Project Group of the Turkish Society of Cardiology in Turkey. The mean age of PH patients was 44.8±5.5 years in SIMURG registry (younger than our patients). Also, the mean age of PH patients in our study was higher than that of PAH patients who were included in another single-center experience at a Turkish university hospital (Ege University) (18). The main difference between our and this study lies in patient characteristics and inclusion criteria.

Most of the patients had severe symptoms at presentation. The proportion of patients belonging to WHO FC III-IV at admission was 54.8% in our study similar to US REVEAL (55%) and Chinese registry (61%); this ratio was higher in other registries (5, 7-9, 15). A large proportion (38.4%) of our study population belonged to WHO FC II. In addition, we had interestingly more number of patients belonging to WHO FC I than to WHO FC IV at admission. Our study population mostly comprised APAH patients. Eisenmenger syndrome patients with a younger age may be the main reason for a high proportion of NYHA I-II patients. Like other registries, there was female predominance (F:M ratio, 2.4). While female patients accounted for 63% of IPAH patients in the NIH registry, it has increased to 80% in the REVEAL registry (5, 6). Our registry reports more female patients than the French registry (71% vs. 62%) (7).

The most commonly reported subtype of PAH is IPAH, followed by APAH, i.e., PAH associated with concomitant disease such as CTD and CHD (7, 10, 14). The proportions range from 39% to 61% for IPAH, 11% to 30% for CTD-PAH, and 10% to 23% for PAH-CHD depending on the registry (3, 7, 10, 14, 19). Unlike these registries, in our study, PAH-CHD was the most frequent subgroup of PAH. In Turkey, CHD is the main and frequent cause of PAH (17). Delay in the diagnosis and treatment of CHD may be the main reason for this distribution in Turkey. Our study showed that we need screening programs for CHD in childhood to decrease the prevalence of PAH-CHD. ASD was the most common congenital defect in PAH-CHD group. Thus, before ASD closure (percutaneous or surgical) at adult age, a detailed echocardiography (both transthoracic and transesophageal) and RHC must be performed. Small, hemodynamically insignificant defects in patients with PAH and irreversible pulmonary artery remodeling (high PVR and negative acute vasodilator response) should be

Table 2. Comparison between different registries and our study group

	US-NIH	REVEAL	French registry	COMPERA	SIMURG	SPANISH	New Chinese Registry	UK	Our study group
Age	36±15	53±14	50±15	65±15	45±6.0	46±18	38±13	50±17	52±16
Sex (Female:Male)	1.7	1.7	1.9	1.5	1.9	2.7	2.3	2.3	2.4
NYHA III-IV (%)	75	73.6	75	91	70	70	61	84	55
IPAH (%)	NA	46.2	39.2	100	34	30	35	NA	46
APAH (%)	NA	50.7	52.7	0	66	31	62	NA	54
6 MWT (m)	NA	374±129	328±112	293±126	NA	382±117	353±127	292±123	353±117

APAH - associated pulmonary artery hypertension; IPAH - idiopathic pulmonary artery hypertension; NYHA - New York Heart Association

avoided to close. Manes et al. (20) showed that PAH after defect correction had the worst prognosis among PAH-CHD group. The proportion of CTD and porto-pulmonary PAH patients was small in our study due to the nature of our hospital (cardiology and cardiovascular surgery branch hospital). We had limited PAH associated CTD and portal HT patients. Thus, we were not able to compare these groups with other PAH groups. Furthermore, the proportion of CTEPH patients in our study was lower than that in SIMURG or other international registries. The differences between our patient population and those of other PAH registries included higher prevalence of APAH-CHD and the absence of hereditary PAH or PAH associated with drugs or toxins in our data.

VR test was positive in only four (2%) patients. This ratio was lower than that reported in SIMURG registry (5%), REVEAL registry (10.2%), and French cohort (10.3%) (6, 7, 17). VR test is recommended only for IPAH, hereditary PAH, and PAH associated with the drug subgroups of PAH. The lower prevalence of VR-positive patients in our study might be associated with lower incidence of these PAH subgroups. VR test was performed with inhale ilioprost in all the patients in our study. Furthermore, high-dose CCB therapy was initiated for VR-positive patients.

Table 2 shows the difference in characteristics between our study population and those of other PAH registries.

The targeted therapy used in this study is monotherapy or goal-oriented sequential combination therapy most of the patients were treated with monotherapy. Bosentan was the most preferred agent for monotherapy in SIMURG (17) and REVEAL (6) registries. Sildenafil was the second most preferred agent. Sequential combination therapy was the most preferred combination therapy (30 of 38 patients). Bosentan remained as the background treatment in cases of double or triple combination therapy. In sequential combination, sildenafil was the first choice as treatment add-on to bosentan followed by ilioprost, similar to REVEAL registry (6). Conversely, in SIMURG registry (16), inhaled ilioprost was the first choice as treatment add-on to bosentan (17). Sildenafil also was the most preferred drug as the second treatment in triple combination therapy. Three of 11 patients receiving triple combination therapy were taking parenteral prostanoid (two i.v. epoprostenol and one s.c. trepostinil). Despite a higher prevalence of patients belonging to WHO FC III-IV, parenteral prostanoid treatment incident was low. The selection of candidates for permanent central venous cannulation has remained an important limiting factor for the initiation of i.v. epoprostenol treatment. The ESC/ERS 2015 PH guidelines have recommended a new upfront combination treatment as an initial therapy (1). Upfront combination was the treatment strategy in 8 of 38 patients receiving combination therapy in our patient population.

Our data will provide important information in real-life settings in terms of demographics, clinical course, PH subgroup distribution, and treatment patterns in patients with PAH in a reference tertiary center in Turkey. Single-center experiences and the following registries are providing valuable information about natural history of diseases, patient demographics, and adherence to current treatment protocols. They constitute the basis for prospective survival studies.

Study limitation

Our data represents a retrospective single-center experience. It does not exactly reflect Turkish PAH patients' population, but there are a lot of similarities (sex, PAH subgroups, WHO FC, treatment choice) with national SIMURG registry. Another limitation of our study is not investigating genetic mutations associated with PAH. Thus, some IPAH patients might have been moved to hereditary PAH subgroups if genetic tests were performed. Furthermore, this data presents PAH experience only from a cardiology perspective. Data from pediatric cardiology, pulmonology, or rheumatology centers should have been incorporated to reflect the real PAH experience in Turkey.

Conclusion

Our data is important to provide information in real-life settings in terms of the demographics, clinical course, PH subgroup distribution, and treatment patterns in patients with PAH in a reference tertiary center in TURKEY. Single center experiences and following registries are giving valuable information about diseases natural history, demographics and adherence of current treatment protocols. They constitute the basis for prospective survival studies.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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Anatol J Cardiol 2018; 20: 35-40
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