Preliminary results from a nationwide adult cardiology perspective for pulmonary hypertension: RegiStry on clInical outcoMe and sUrvival in pulmonaRy hypertension Groups (SIMURG)

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Abstract

Objective: The present study was designed to evaluate the characteristics of pulmonary hypertension (PH) and adult cardiology practice patterns for PH in our country.

Methods: We evaluated preliminary survey data of 1501 patients with PH (females, 69%; age, 44.8±5.45) from 20 adult cardiology centers (AdCCs).

Results: The average experience of AdCCs in diagnosing and treating patients with PH was 8.5±3.7 years. Pulmonary arterial hypertension (PAH) was the most frequent group (69%) followed by group 4 PH (19%), group 3 PH (8%), and combined pre- and post-capillary PH (4%). PAH associated with congenital heart disease (APAH-CHD) was the most frequent subgroup (47%) of PAH. Most of the patients' functional class (FC) at the time of diagnosis was III. The right heart catheterization (RHC) rate was 11.9±11.6 per month. Most frequently used vasoreactivity agent was intravenous adenosine (60%). All patients under targeted treatments were periodically for FC, six-minute walking test, and echo measures at 3-month intervals. AdCCs repeated RHC in case of clinical worsening (CW). The annual rate of hospitalization was 14.9±19.5. In-hospital use of intravenous iloprost reported from 16 AdCCs in CWs. Bosentan and ambrisentan, as monotreatment or combination treatment (CT), were noted in 845 and 28 patients, respectively, and inhaled iloprost, subcutaneous treprostinil, and intravenous epoprostenol were noted in 283, 30, and four patients, respectively. Bosentan was the first agent used for CT in all AdCCs and iloprost was the second. Routine use of antiaggregant, anticoagulant, and pneumococcal and influenza prophylaxis were restricted in only two AdCCs.

Conclusion: Our nationwide data illustrate the current status of PH regarding clinical characteristics and practice patterns.

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Keywords: pulmonary hypertension, preliminary survey data of Turkey

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Introduction

Pulmonary hypertension (PH) is a progressive and usually fatal disease characterized by the development of concentric remodeling, vasospasm, and in situ thrombosis within small pulmonary arteries. It usually increases pulmonary vascular resistance and pulmonary arterial pressure (PAP) and results in severe right ventricular and atrial dysfunction (1–15).

The Pulmonary Vascular Diseases Project Group (PVDPG) of the Turkish Society of Cardiology (TSC) has been established as a nationwide initiative with the aim of providing an adult cardiology perspective for PH in Turkey. More than 20 adult cardiology centers (AdCCs) from across the country currently participate in this network. The first action of PVDPG has been the design of a nationwide study, the RegiStry on clInical outcoMe and sUrvival in pulmonaRy hypertension Groups (SIMURG). The aim of the present study was to demonstrate the main characteristics of PH groups and to evaluate the current practice patterns of AdCCs and the problems in multidisciplinary teamwork regarding the diagnosis and management of patients with PH as determined from the initial survey data of AdCCs that have participated in the SIMURG registry. The first aim of SIMURG was to provide information in real-life settings in terms of the demographics, clinical course, PH subgroup distribution, and treatment patterns in patients with pulmonary arterial hypertension (PAH) in Turkey. The second aim was to establish the suitability of PH referral centers in Turkey mentioned in the guidelines.

Methods

The SIMURG registry is a retrospective, multicentre, observational, Turkey-based study of 1501 patients with PH from 20 AdCCs. This study was based on preliminary results from the survey of AdCCs participating in the SIMURG registry and included data from participating AdCCs obtained from online responses to a simple questionnaire. The researchers in charge at each centre were selected from members of the Turkish Society of Cardiology (TSC) Pulmonary Vascular Diseases Project Group (PVDPG). AdCCs participating in the SIMURG registry are listed in Table 1. The average experience of AdCCs was 8.5 years.

The centers declared that their institutional experiences were presented at international meetings or published as papers

Table 1. Age, sex, and patient number data from the adult cardiology centers in each subgroup

Adult cardiology center	Experience of center (year)	Patient number	Female (%)	Age, mean	Group 1 (%)	IPAH[a] (%)	Congenital heart disease (%)	Connective tissue disease number (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)
Dokuz Eylül 16	7	92	70 (76)	52	74 (80)	27 (36)	33 (45)	14 (19)	0	0	18 (20)
KATU 1	6	45	36 (80)	49	40 (89)	13 (32)	24 (60)	1 (3)	0	2 (5)	3 (7)
Koşuyolu 18	9	309	181 (59)	46	200 (65)	53 (26)	131 (66)	16 (8)	12 (4)	39 (12)	58 (18)
Marmara 17	6	132	68 (52)	55	28 (21)	3 (11)	15 (54)	10 (36)	0	0	104 (79)
Gazi 9	9	40	36 (90)	56	36 (90)	8 (22)	21 (58)	12 (33)	0	0	4 (10)
Fırat 3	8	54	41 (64)	40	52 (96)	27 (51)	13 (25)	12 (23)	0	0	2 (4)
Dicle 5	4	42	27 (64)	45	39 (92)	8 (20)	29 (74)	2 (5)	0	0	3 (7)
Hacettepe 11	20	125	90 (72)	47	105 (84)	41 (39)	14 (13)	50 (48)	0	0	20 (16)
İnönü 4	5	16	14 (88)	41	16 (100)	4 (25)	11 (68)	1 (6)	0	0	0
Atatürk 2	8	35	20 (57)	35	22 (62)	5 (22)	15 (68)	2 (9)	0	0	13 (37)
Çukurova 6	10	21	17 (81)	40	19 (90)	6 (32)	6 (32)	7 (37)	0	0	2 (9)
Osmangazi 13	15	9	7 (78)	40	8 (89)	3 (38)	5 (63)	0	1 (11)	0	0
Uludağ 14	12	56	38 (68)	40	49 (88)	8 (17)	25 (51)	16 (33)	0	0	7 (13)
Ege 21	8	114	69 (61)	47	96 (84)	23 (24)	64 (67)	9 (9)	0	5 (4)	13 (11)
Erciyes 7	8	23	16 (69)	41	20 (86)	0	16 (80)	1 (5)	0	0	3 (13)
TYIH 12	9	63	42 (67)	43	43 (68)	26 (60)	15 (34)	1 (2)	2 (15)	2 (3)	16 (25)
Haseki 19	7	104	72 (69)	48	98 (94)	30 (24)	68 (65)	0	0	0	6 (6)
Gaziantep 23	6	46	15 (33)	40	45 (99)	18 (40)	27 (60)	0	0	0	1 (2)
Cerrahpaşa 20	8	143	103 (72)	46	109 (76)	48 (44)	17 (16)	44 (40)	16 (11)	2(1)	16 (11)
Cumhuriyet 8	6	32	22 (68)	45	25 (78)	20 (80)	4 (16)	1 (4)	2 (11)	1 (3)	4 (12)
All patients	8.5	1501	984 (69)	44.8	1124 (74)	371 (33)	553(49)	199 (18)	33 (3)	51 (4)	293 (19)

a - idiopathic pulmonary arterial hypertension

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Table 2. The patient numbers with group 1, vasoreactivity rates, targeted drug utilization characteristics and the rates of hospitalizations due to clinical worsening (patient/year)

	Group 1 number (%)	VR + number (%)	Group 4 number (%)	ERA[a] number (%)	PD5i[b] number (%)	PGI2[c] number (%)	Hospitalization patient/year (%)
Dokuz Eylül 16	74 (80)	2 (3)	18 (20)	36 (39)	3 (3)	7 (8)	12
KATU 1	40 (89)	4 (10)	3 (7)	43(100)	11(25)	32 (74)	10
Koşuyolu 18	200 (65)	0	58 (18)	172 (66)	68 (26)	63 (24)	90
Marmara 17	28 (21)	0	104 (79)	27 (20)	15 (12)	30 (23)	10
Gazi 9	36 (90)	3 (8)	4 (10)	38 (95)	10 (25)	16 (40)	4
Fırat 3	52 (96)	1 (2)	2 (4)	51 (96)	4 (7)	3 (6)	5
Dicle 5	39 (92)	0	3 (7)	7 (16)	1 (2)	3 (5)	15
Hacettepe 11	105 (84)	5 (5)	20 (16)	49 (39)	27 (22)	31 (24)	2
İnönü 4	16 (100)	0	0	14 (88)	7 (43)	10	4
Atatürk 2	22 (62)	3 (14)	13 (37)	34 (97)	4 (11)	5 (13)	7
Çukurova 6	19 (90)	3 (15)	2 (9)	15 (71)	1 (5)	7 (33)	12
Osmangazi 13	8 (89)	1 (12)	0	6 (75)		1 (13)	4
Uludağ 14	49 (88)	10 (20)	7 (13)	47 (84)	2 (4)	29 (51)	3
Ege 21	96 (84)	0	13 (11)	90 (94)	35 (36)	19 (20)	30
Erciyes 7	20 (86)	5 (25)	3 (13)	15 (65)	3(13)	7 (30)	1
TYIH 12	43 (68)	0	16 (25)	45 (76)	14 (23)	24 (42)	15
Haseki 19	98 (94)	4 (-)	6 (6)	63	12	13	24
Gaziantep 23	45 (99)	0	1 (2)	44 (96)	17 (37)	3 (7)	20
Cerrahpaşa 20	109 (76)	0	16 (11)	52 (41)	12 (10)	9 (7)	25
Cumhuriyet 8	25 (78)	6 (24)	4 (12)	25 (87)	0	19 (65)	5
Overall	1124 (79)	52 (5)	293 (21)	873 (67)	256 (20)	331 (25)	15

a - Endothelin receptor antagonist; b - Phosphodiesterase type 5 inhibitor; c - Prostocyclin analogues

in peer-reviewed journals. A total of 15 centers had participated in national PH registries, including THALES, OPTION, and the Turkish Thoracic Society, and seven centers had participated in the multicentre international PROPEL registry or CHEST, PATENT, GRIPHON, and SERAPHIN world-wide multicentre randomized trials. Twelve centers had extracorporeal membrane oxygenation (ECMO) facilities, four were capable of performing pulmonary endarterectomy, three were capable of performing lung transplantation, and 18 were capable of performing complex heart surgery.

Inclusion criteria was being diagnosed as with PH on the basis of the diagnostic criteria of the American College of Cardiology/American Heart Association (AHA/ACC) 2009 and the European Society of Cardiology/European Respiratory Society (ESC/ERS) 2009 Guidelines (12, 13). Patients with pure postcapillary (i.e., group 2) PH were excluded from the study because of the low numbers of pure postcapillary patients prior to the enrolment phase.

The clinical and hemodynamic definitions and classification of PH followed the criteria of AHA/ACC 2009 and ESC/ERS 2009 Guidelines (12, 13). PH was defined as a hemodynamic and pathophysiological condition characterized by an increase in mean PAP >25 mm Hg at rest, as assessed by right heart catheterization (RHC). Precapillary PH was defined as the presence of a mean PAP of >25 mm Hg, with pulmonary wedge pressure (PWP) of <15 mm Hg and normal or reduced cardiac output. Conversely, postcapillary PH was defined as a mean PAP of >25 mm Hg with PWP of >15 mm Hg and normal or reduced cardiac output (12, 13). Passive and reactive (out of proportion) PH was defined by a transpulmonary gradient (TPG) of <12 mm Hg and TPG of >12 mm Hg, respectively. A vasoreactivity test (VRT) was performed to determine the calcium channel blocker responders in drug-associated idiopatic pulmonary arterial hyrpertension (IPAH), heritable pulmonary arterial hypertension (HPAH), and PAH. A positive vasodilator response was defined as a reduction in the mean PAP of >10 mm Hg, leading to a value of <40 mm Hg, with a normal or high cardiac output.

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

Statistical methods

Descriptive statistics were reported as mean±standard deviations for continuous data. Categorical variables were shown

as frequency and percentage. Descriptive statistical analysis was performed using SPSS® Statistics version 20.0 (IBM SPSS Statistics for Mac, IBM Corp., NY).

The authors of this trial have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

Results

Data derived from each AdCC are summarized in Table 1 and Table 2.

Institutional characteristics

The average experience of AdCCs since their organization as multidisciplinary PH centers (with capabilities for diagnosis, targeted therapy, and surgery) was 8.5±3.7 years (ranging from 3 to 20 years) (Table 1). Institutional contributions to the overall study population are demonstrated in Table 1. Brain natriuretic peptide (BNP) (12 centers) or N-terminal Pro-BNP (six centers) were used for risk assessment. The capacities for ECMO, pulmonary endarterectomy (PEA), complex congenital heart surgery, and lung transplantation surgery were documented as available in 12, four, 18, and three of the 20 AdCCs, respectively.

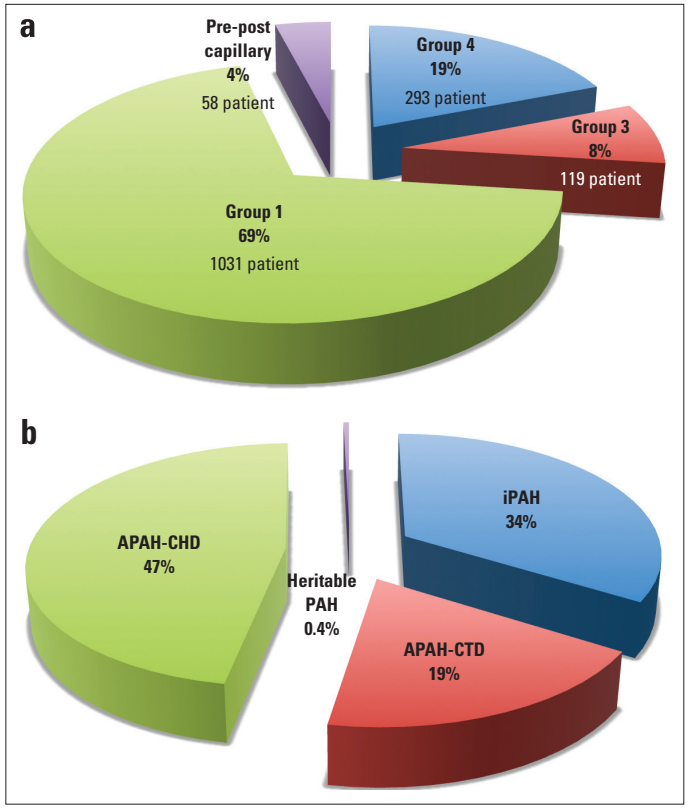

Figure 1. (a) The group distribution in overall patients with pulmonary hypertension. (b) Subgroups in PAH group

IPAH - idiopathic pulmonary arterial hypertension; APAH-CTD - connective tissue disease associated pulmonary arterial hypertension; APAH- CHD - congenital heart disease associated pulmonary arterial hypertension

Patient characteristics

The mean age of the patients was 44.8±5.5 years (ranging from 14 to 89 years), and females accounted for 69% of all patients (Table 1). The age range and sex distribution seemed to be homogenous across AdCCs (Table 1). Group 1 PH, i.e., PAH, was the most frequently encountered PH group (69%), followed by chronic thromboembolic pulmonary hypertension (CTEPH) (19%), group 3 PH (8%), and combined pre- and post-capillary PH (formerly "out of proportion" PH) (4%) (Fig. 1a). A subgroup analysis of group 1 PH patients revealed an association between PAH and congenital heart disease (APAH-CHD) as the most frequent etiology (47%), whereas IPAH, PAH associated with connective tissue disease (APAH-CTD), and HPAH were noted in 34%, 19%, and 0.4%, respectively, of the overall patients with PAH (Fig. 1b). Group 3 PH with precapillary severe PH was frequent in two AdCCs, but rare or not reported in other AdCCs. CTEPH was more frequent in two AdCCs that had established a high-volume collaborative surgical PEA program (Table 1).

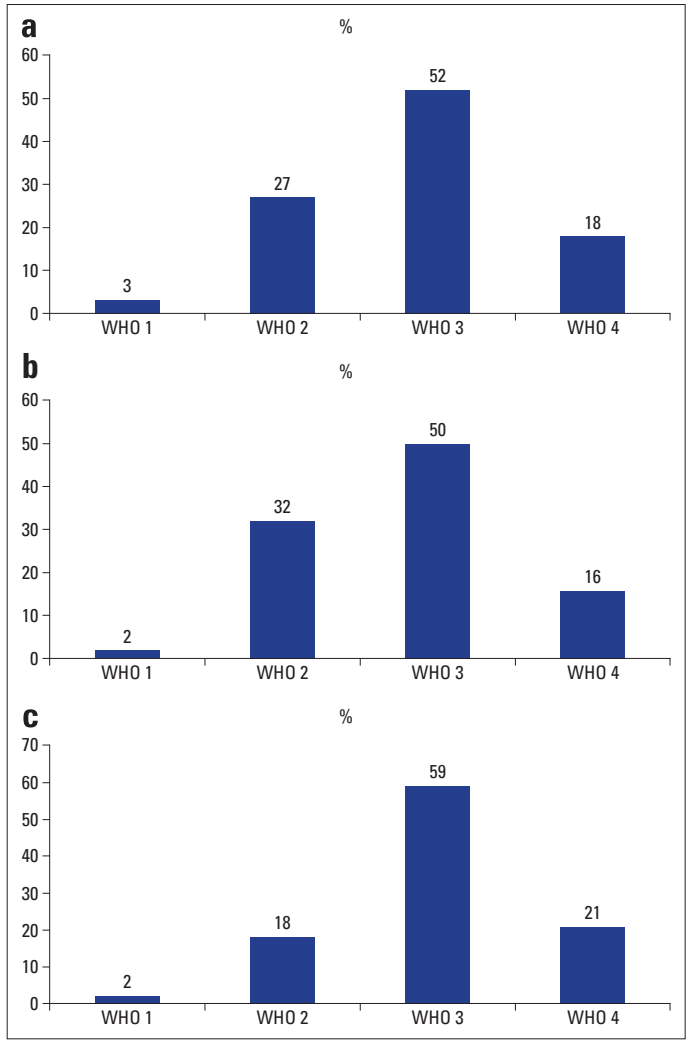

Figure 2. (a) Functional class of all patients with PH at the time of diagnosis. (b) Functional class of PAH subgroup patients at the time of diagnosis. (c) Functional class of CTEPH subgroup patients at the time of diagnosis

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Functional class of patients at diagnosis

The World Health Organization (WHO) functional class (FC) statuses for the whole PH population and PAH and CTEPH groups are demonstrated in Figures 2a–c respectively. At the time of diagnosis, 18%, 52%, 27%, and 3% of the PH population of the study were WHO FC IV, III, II, and I, respectively (Fig. 2a). Similarly, in the PAH group, 16%, 50%, 32%, and 2% were WHO FC IV, III, II, and I, respectively (Fig. 2b). These FC patterns in PH and PAH groups showed no significant variation among the various AdCCs. The predominance of WHO FC III status was more prominent in patients with CTEPH, where 21%, 59%, 18%, and 2% were WHO FC IV, III, II, and I, respectively (Fig. 2c).

Catheterization procedures at diagnosis

The mean rate of RHC procedures with or without left heart catheterization was 11.9±11.6 per month per center (RHC ranging from 1 to 45 per month per center) (Fig. 3). Our aim was to determine the number of RHC procedures per month to check the availability of AdCCs to serve as referral centers. Initial RHC was performed in all patients for diagnosis.

A vasoreactivity test (VRT) was performed with the following agents: adenosine administered intravenously over 2 min at 50–350 mg/kg/min, nitric oxide (NO) administered by inhalation over 5 min at 10–20 ppm, epoprostenol administered intravenously over 10 min at 2–12 mg/kg/min (a dosage range recommended in the current guidelines).

The most frequently used agent was intravenous adenosine (in 60% of AdCCs), followed by inhaled iloprost (30%) and inhaled NO (only 10%). The mean positive VRT was 5% (Table 2).

Follow-up management

In general, follow-up of patients with PH was conducted in accordance with the recommendations of the ESC/ERS 2009 PH guidelines. The rules of the Social Security Agency for reimbursement of PH-targeted treatments resulted in all patients under the targeted treatments being assessed periodically at 3-month intervals. FC assessment, a six-minute walking test, and Doppler echocardiography were routinely performed during these periodic assessments. All 20 AdCCs repeated RHC in cases of clinical worsening (CW), whereas RHC was performed at 2-year intervals in two AdCCs, and annually in three AdCCs in the absence of CW. The mean rate of patient hospitalization due to CW episodes was 14.9%±19.5% per year.

Targeted treatments

The targeted agents used in this study as monotherapy or as part of a goal-oriented sequential combination treatment are summarized in Figure 4.

Endothelin receptor antagonists (ERA): Bosentan and ambrisentan were used as monotherapy or as a component of a combination treatment in 845 and 28 patients, respectively.

Prostacyclins: Inhaled iloprost, subcutaneous treprostinil (scTREP), and intravenous epoprostenol were used in 283, 30, and four patients, respectively (Fig. 4). During severe CW, off-label, in-hospital and short-term use of intravenous iloprost was reported in 16 AdCCs.

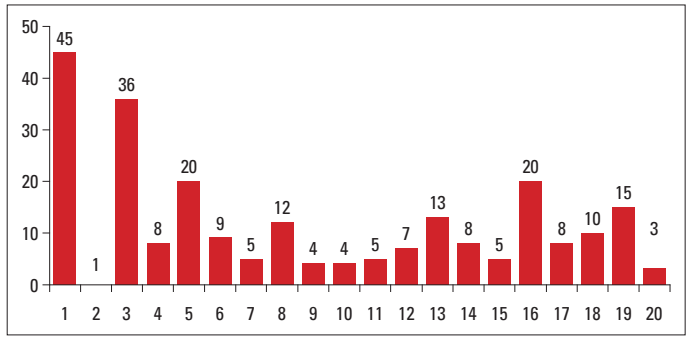

Figure 3. Right heart catheterization rates per month from 20 adult cardiology centers. The mean rate of right heart catheterization procedure was 11.9±11.6 per month (ranging from 1 to 45 per month)

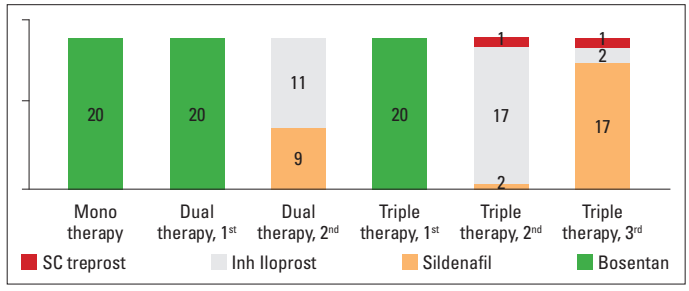

Figure 4. Overall preferences for initial monotherapy and sequential combinations

Treatments targeting the nitric oxide pathway: Sildenafil was used in 265 patients, whereas tadalafil was not available for PH treatment in our country at the time of patient enrolment. The soluble guanylate cyclase stimulator riociguat was used in 16 patients (Fig. 4). The PAH-targeted treatment choices for initial monotherapy and sequential combinations are presented in Figure 4. In the absence of any severe adverse event requiring cessation of therapy, all AdCCs preferred to maintain the background treatment(s) together with the addition of other specific drugs targeted at different pathways as second or third agents. Bosentan was the first choice of monotherapy in all AdCCs. Inhaled iloprost was the second drug used in double and triple combinations, whereas sildenafil was noted as a second choice in combinations. The utilization of scTREP was limited, as it was used in one center as the second or third drug choice in a triple combination administered to deteriorating patients.

Non-targeted treatments and vaccinations

Routine use of an antiplatelet and an oral anticoagulant was documented in six and three AdCCs, respectively. Routine pneumococcal vaccinations were performed in 18 AdCCs and influenza prophylaxis in 19 AdCCs.

Discussion

The preliminary results of the SIMURG survey should be viewed as an attempt to illustrate the adult cardiology

perspective for PH in Turkey, based on the records of 1501 patients with PH from 20 AdCCs distributed in different geographical parts of Turkey. The aim of SIMURG was to provide information about the demographics, clinical courses, subgroup distributions, and treatment patterns of the referral centers, as recommended in the guidelines. The guidelines recommend that a referral center should follow at least 50 patients, with two new referrals per month with documented PAH or CTEPH, and the center should also perform at least 20 vasoreactivity tests in patients with PAH per year and participate in collaborative clinical research on PAH, which includes phase II and phase III clinical trials. Referral centers are required to provide care through a multiprofessional team (cardiology and respiratory medicine physicians, clinical nurse specialists, radiologists, psychological and social work support, and appropriate on-call expertise), as well as to have direct links and quick referral patterns to other services (such as CTD, family planning, PEA, lung transplantation, and adult congenital heart disease services).

Some regional differences were evident in terms of the duration of experience with PH, the size of the patient population, and the facilities related to various problems of severe PH, including ECMO, PEA, complex congenital heart surgery, and lung transplantation surgery. Some AdCCs have presented or published their institutional experiences on PH practice in international peer-reviewed journals (16–31). The majority of AdCCs have participated in national PH registries, while seven AdCCs participated in international registries or world-wide multicentre RCTs. From the results, we identified that 10 AdCCs could not reach the recommended patient number or vasoreactivity tests.

The main characteristics of patients with PH regarding female predominance and mean age showed high concordance across AdCCs and did not differ from those reported in modern PH studies (1–11). The most frequent subgroup in our PAH population was APAH-CHD, with a proportion of 47%, which was higher than that in the REVEAL cohort (19.5%) or the French cohort (15.3%). This predominance of APAH-CHD in the PAH population seems to be homogeneous, except for two AdCCs in which the frequency of APAH-CTD was relatively higher than that in the others. The difference between our survey data and other contemporary PAH registries were striking in terms of the significantly higher prevalence of APAH-CHD and the absence or infrequency of HPAH or PAH associated with drugs or toxins in our data (1–11). This situation can be explained by several factors. The mean age of patients was lower than that in the REVEAL registry (mean age, 53) and the French cohort (mean age, 50), which may be explained by the higher rates of APAH-CHD in Turkey. PAH associated with drugs was not reported in our population, unlike the case for the REVEAL registry (10.5%) and the French cohort (9.5%). This could be a consequence of the restricted usage of anorexigens in Turkey when compared to developed countries.

We documented the combined pre- and post-capillary PH, as defined by the criteria of the ESC/ERS 2009 PH guidelines, in 4% of the patients (12). More recent guidelines are now available for this classification, but the 2009 guidelines were used at the time of establishment of the registry. These patients with PAH were documented as being of older age and having obesity and multiple comorbidities associated with elevated left ventricle filling pressures (32).

Group 4 PH, with precapillary severe PH, was frequent in two AdCCs (number 3 and 4); however, it was rare or not reported in other AdCCs. These two AdCCs had a high-volume collaborative surgical PEA program. The current guidelines recommend the referral of patients with CTEPH to expert CTEPH centers (15, 33–35). The formation of a collaborative network between a university hospital and a high-volume education and training hospital has resulted in a progressive decrease in the perioperative mortality rate to below 5%–10% (19).

In our survey, at the time of diagnosis, 18%, 52%, 27% and 3% of the overall patients with PH were WHO FC IV, III, II, and I, respectively. Similarly, most patients in the PAH group were WHO FC III (50%) or II (32%), whereas 16% of the patients were WHO FC IV. More importantly, the FC patterns for PH and PAH showed no significant variation across the participating AdCCs. Patients with WHO FC III-IV status were noted in 70%–80% of the overall PAH cohorts in the contemporary series (71% of cases in the Portugal Registry, 73% in the REVEAL registry, and 75% in the French Registry were WHO FC III or IV) (1–11). With no significant difference between subgroups, the results demonstrated a noteworthy time delay for diagnosis, which is similar to the delays reported in other modern registries (1–11).

In our data, the RHC performance rate (with or without left heart catheterization) procedure was 11.9±11.6 patients per center per month (ranging from 1 to 45 per month). Our data indicate that the follow-up strategy adopted in accordance with previous ESC/ERS PH guideline recommendations is also consistent with those of the new PH guidelines. The rules of the Social Security Agency for reimbursement of PH-targeted treatments require that all patients under targeted PAH treatments be reassessed at 3-month intervals. All AdCCs repeated the RHC in cases of CW, whereas RHC was performed regularly at 2 year intervals in two AdCCs, and annually in three AdCCs, even in the absence of CW.

Our data showed that intravenous adenosine was the most frequently used agent, followed by inhaled iloprost and inhaled NO, whereas intravenous epoprostenol was not used. The positive VRT response rate was around 5%, and our nationwide practice for VRT agents seems to be more consistent with the recommendations of the new PH guidelines compared with those of the previous guidelines (15). VRT was lower than that in the REVEAL registry (10.2%) and French cohort (10.3%), which may reflect the lower incidence of IPAH, HPAH, and PAH associated with the drug subgroups in Turkey.

Targeted treatment patterns of AdCCs in patients without positive VRT responses seem to represent the availability of specific agents at the time of initiation of treatment. Uniformly, bosentan was the first choice in monotherapy, similar to the

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REVEAL registry, and it remains as the background treatment in cases of double and triple combination therapies. Inhaled iloprost was the first choice as a treatment add-on to bosentan in double combinations, followed by sildenafil; this contrasted with the situation of the REVEAL registry. In triple combinations, sildenafil was the most preferred drug as the second treatment, while inhaled iloprost was the third treatment of choice added to bosentan and sildenafil. Ambrisentan was a new ERA and sitaxentan was a withdrawn agent, whereas tadalafil, macitentan, riociguat, and selexipag were not available as treatment modalities in AdCCs at the time of enrolment. Similar to our survey data, the French registry reported that bosentan was the most frequently used drug in both the incident and overall PH cohort, followed by sildenafil and inhaled iloprost (4, 5). A combination of targeted therapies was reported in 3.6% and 12.6% of the incident PAH and overall cohorts of the same registry, respectively (4, 5). The REVEAL registry reported that ERA was used in 38.5% and PDE5i in 46% of the overall cohort (10, 11).

Our combination practice was based on the goal-oriented treatment algorithm of previous PH guidelines (36). However, the ESC/ERS 2015 PH guidelines have recommended a new upfront combination treatment algorithm in patients without a positive VRT response (15). In our survey data, the commonly used sequential combinations were inhaled iloprost or sildenafil added to a background bosentan treatment. The new PH guidelines proposed a new algorithm for sequential combinations, but the level of evidence for these "game-changing" recommendations needs to be improved from level C evidence to higher levels (15).

The new PH guidelines recommend intravenous epoprostenol as an agent for patients with WHO FC IV and III (IA) because of its proven survival benefit. An initial double combination therapy with intravenous epoprostenol and bosentan or a triple combination with intravenous epoprostenol, bosentan, and sildenafil should be considered for patients with WHO FC III and IV (15). Intravenous epoprostenol treatment was reported in 17.9% of patients with incident PAH and in 14.7% of overall PAH cohorts in the French registry, while the REVEAL registry documented an overall use of intravenous epoprostenol of 19.7% and up to 35.5% in patients with WHO FC IV (4, 5, 10, 11). Despite the high frequency of WHO FC III-IV status in our population, intravenous epoprostenol treatment was not documented in our initial data, and only one AdCC reported subcutaneous treprostinil as a second agent in double combinations or as a third agent in triple combinations in patients needing more potent treatments. The reasons for this discrepancy seem to be multifactorial. At the time of enrolment into the registry, the experience with the thermolabile form of intravenous epoprostenol (Flolan©) was limited, and its thermostable form (Veletri©) was not available in our country.

The selection of candidates for permanent central venous cannulation has remained an important limiting factor for the initiation of intravenous epoprostenol treatment. Consequently, subcutaneous treprostinil has been used as an alternative in compliant patients. Barst et al. (37) reported that subcutaneous treprostinil monotreatment was associated with 70% 4-year survival and 79% 5-year survival rates in patients with PAH. REVEAL data documented the overall use of subcutaneous or intravenous treprostinil as monotherapy or part of combination in 14.6% of patients with WHO FC III and 7.1% of those with WHO FC IV (10, 11). The ESC/ERS 2015 PH guidelines have recommended initial subcutaneous treprostinil monotherapy for patients with WHO FC IV (IIbC) and FC III (IB). However, retrospective analysis of the deaths in the REVEAL registry showed that parenteral prostacyclin treatments in high-risk patients remains an unmet need, even in the US, where PH expert centers and referral patterns have been established (38).

Our preliminary data indicated a mean rate of hospitalization due to CW episodes of 14.9±19.5 per year, and this may translate into persistence of deterioration and a worse mid-to long-term outcome (15). During CW episodes, the use of off-label, in-hospital, and short-term use of intravenous iloprost was reported for clinical stabilization in 16 AdCCs. This treatment has been indicated for PAH in New Zealand and has been used as an off-label chronic treatment in some European countries. Outpatient treatment with intravenous iloprost has been recommended as a new option for patients with WHO FC III (Class IIa C) and FC IV (Class IIb C) in the ESC/ERS 2015 PH guidelines (15) and may be considered as an important step for the generalization of this treatment.

The routine use of an antiplatelet and an oral anticoagulant were limited. The new PH guidelines suggest that an oral anticoagulant treatment may be considered in patients with IPAH, HPAH, and PAH due to the use of anorexigens (Class IIb C) (15). Consistent with the Class IC recommendations of the new PH guidelines, the majority of AdCCs routinely administered pneumococcal vaccinations (15).

The subsequent phase of the complete SIMURG registry included the adoption of new criteria indicated in the consensus statement of the Nice 5th World Symposium on PH. The upcoming SIMURG registry data is expected to provide more comprehensive prospective data in many areas, including novel diagnostic and prognostic algorithms, standards of PH expert centers and referral patterns of these centers, follow-up management, and evidence-based treatment patterns in PH populations.

Study limitations

The main issues that AdCCs need to overcome appear to be difficulties in the coordination of the multidisciplinary relations in terms of the differential diagnosis of PH subgroups and reassessment during follow-up, the lack of specialized services and intensive care units dedicated to PH, and the lack of well-experienced nursing and rehabilitation teams. In cardiology, the limited number of pulmonologists, rheumatologists, radiologists, and nuclear physicians interested in PH makes a multidisciplinary approach even harder. Time delay in the approval and reimbursement of the off-label targeted PH treatments by the Social Security Agency and the Ministry of Health is another issue, which

may have an unfavorable effect on patient health. The present analysis is limited to the initial results of survey data obtained from 20 AdCCs, whereas data from centers based on pediatric cardiology, pulmonology, or rheumatology have not been incorporated. This paper may also represent the former practice patterns in this setting.

Conclusions

The preliminary analysis of the SIMURG survey data illustrates the current status of nationwide practice patterns of PH, from diagnosis to management, as reported by 20 AdCCs. These results may provide a valuable roadmap to improve evidence-based, nationwide, and multidisciplinary approaches to PH. The adherence to recommendations of the new PH guidelines, the quality standards of AdCCs, the multidisciplinary networks, the referral patterns to expert centers, and the participation in international multicentre studies need to be improved.

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