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Original Research Article

Eight Years of Experience in Our Pulmonary Arterial Hypertension Center/ Van / Turkey

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Aim: Pulmonary hypertension (PH) is a progressive pulmonary vascular disease characterized by pulmonary artery remodeling and vasoconstriction resulting in elevated pulmonary arterial pressure and consequent right heart failure. In this study, we aimed to present our single center clinical experience with these patients. ***Method*****:** 331 patients who were followed up in our center with the diagnosis of pulmonary arterial hypertension between 2013-2021 were evaluated by retrospective analysis method. ***Results*****:** The mean age of the patients was 54.6, mean sPAB value was 75.4 mmHg and the mean follow-up period of the patients was recorded as 44.9 months. It was determined that 68.9% of them were female. When the etiological diagnoses were evaluated in order of frequency; congenital heart disease, chronic thromboembolic pulmonary hypertension (CTEPH), idiopathic pulmonary arterial hypertension (IPAH), collagen tissue disease, disproportionate pulmonary hypertension (group 2, group 3) and rare cases (pulmonary veno-occlusive disease (PVOD), portal hypertension (PoHT)). When the survival analysis is evaluated, the risk of mortality increases 1.021 times as the age increases. Men have a 1,863 times higher risk of mortality than women. The mortality risk of those with a congenital diagnosis is 0.36 times less than those with a diagnosis of IPAH. Negative correlation was found between functional class of patients and mortality ($p<0.005$). The risk of mortality increases 1.016 times as the SPAB increases. ***Conclusion*****:** "Pulmonary hypertension is a disease with high mortality and includes different disease groups". The follow-up of these patients in PAH centers and the use of special medications affect mortality rates.

Keywords: Pulmonary arterial hypertension; Pulmonary, hypertension, Right heart failure; Epidemiology; Survival.

INTRODUCTION

Pulmonary hypertension (PH) is a progressive pulmonary vascular disease characterized by remodeling and vasoconstriction in the pulmonary arteries, resulting in elevated pulmonary arterial pressure and consequent right heart failure [1, 2]. In the PH meeting held in 2018, a mean PAP>20 mmHg, pulmonary artery wedge pressure (PAWP) <15 mmHg and pulmonary vascular resistance (PVR)>3 WU were defined as PH [2]. Disease groups causing PH were arranged in the same symposium as shown in Table 1. Pulmonary Hypertension includes a spectrum of diseases divided into 5 groups: Group 1, pulmonary arterial hypertension (PAH); group 2, PH due to left heart disease (LHD); group 3, PH due to lung disease; group 4, chronic thromboembolic PH (CTEPH); and group 5 is defined as pulmonary hypertension with unclear multifactorial mechanisms. For the treatment and management of pulmonary hypertension caused by various reasons, all reasons should be investigated with a multidisciplinary approach and treatment plans should be established. Regardless of the cause of pulmonary hypertension, mortality is high especially in group 1 PAH patients [3]. In idiopathic PAH, the mean life expectancy after diagnosis without treatment is 2.8 years [4]. In addition to the course of the disease, early diagnosis has a high contribution to mortality [5].

A multidisciplinary approach is required for the treatment and management of pulmonary hypertension caused by various causes, and therefore pulmonary arterial hypertension (PAH) centers have been established.PAH centers have been established to find the etiology of these patients, observe and treat them at an early stage. The definition of the pulmonary arterial hypertension referral center was made in 2009 at esc [6]. Characteristics of PAH center shown in Table 2 [6, 7, 2]. These figures can be adapted to the characteristics of each country like population distribution, geographical limitations, etc.). Our clinical

experience in pulmonary hypertension patients who are followed up at Yüzüncü Yıl University Faculty of Medicine PAH center will be presented in this study.

METHOD

This study was planned retrospectively. Demographic, etiological, treatment, clinical parameters (functional class, Pulmonary arterial pressure values) and survival information of pulmonary hypertension patients followed up in the PAH center of Yüzüncü Yıl University between 2013-2021 were obtained from the hospital registry system. In diagnosis and classification, the Updated Pulmonary Hypertension Classification published by ESC in 2018 was adhered to (Table 1) [2]. The clinical features of the patients were evaluated for each class by evaluating the laboratory parameters and additional examinations. The factors affecting survival were evaluated by performing a survival analysis.

Statistical Method

Data were analyzed with IBM SPSS V23. Conformity to normal distribution was evaluated with the Kolmogorov-Smirnov test. Chi-square test was used to compare categorical variables according to groups. Independent two-sample T-test was used to compare normally distributed data according to paired groups, and Mann-Whitney U test was used to compare non-normally distributed data. Kruskal Wallis test was used to compare the data that were not normally distributed according to groups of three or more, and multiple comparisons were examined with Dunn's test. The independent risk factors affecting the survival time were analyzed by Cox Regression analysis. Log Rank (Mantel-Cox) test was used to determine whether there was a difference between survival times depending on the variables. Analysis results were presented as mean ± standard deviation and median (minimum – maximum) for quantitative data, and frequency (percent) for categorical data. Significance level was taken as $p<0.050$.

RESULTS

The mean age of the patients was 54.6 (min 15, maximum 95), and the mean systolic pulmonary artery pressure (sPAP) value was 75.4 mmHg (min 29 - max 160). The mean follow-up period of the patients was recorded as 44.9 months (min 2 months, maximum 90 months) (Table 3). Although the frequency distribution of the categorical data is shown in Table 2, when the prominent results are evaluated 63.1% of the patients are in the 50 and over age group. It was found that 68.9% of patients were women and 33.2% were diagnosed with congenital heart disease. 75.7% of the patients used a single medication, 29.6% had endothelin receptor antagonist as first medication, 44.6% had endothelin receptor antagonist as second medication, 70.8% had phosphodiesterase-5 inhibitors as third medication. It was found that 16% of the patients followed during the 8-year period were EX. It was found that 56.5% of the patients followed were functional class II and 24.8% of them were diagnosed in 2018. It was observed that the number of new patients decreased in 2019-2020-2021 (respectively (14.5%, 5.7%, 4.2%)). When the etiological diagnoses were evaluated, 33.2% (n: 110) congenital heart disease, 25.7% (n:85) CTEPH, 13.9% (n:46) IPAH, 9.1% (n:30) collagen tissue disease, 16.3% (n:54) disproportionate pulmonary hypertension, 1.8% (n) :6) rare cases (venoocclusive disease, portal hypertension) was observed (Figure 1). In addition, when the sub-diagnoses were examined it was observed that 31.7% of the patients had cardiac shunt, 29.9% (n:) had idiopathic PAH, 16.3% had lung disease, 5,7% had hereditary PAH, 5.7% had scleroderma, 1.8% had pulmonary venous return anomaly, 1.5% had Behçet's disease, 1.2% had renal failure, 0.9% had SLE, 0.6 % had sarcoidosis, 1% had glycogen storage disease, 1% had IPF, %1.2 pulmonary veno-occlusive disease (PVOD), % 0.6 portal hypertension. 75.7% of the patients used one medication, 16.3% two medications, 8% three medications. It was found that 40.8% of the patients using medications used endothelin receptor antagonists and 29% used calcium channel blockers.

Although the comparison of categorical data according to diagnoses is shown in Table 4, a statistically significant difference was found between the distribution of patient age groups according to diagnoses when the prominent data were evaluated ($p<0.001$). 84.8% of those with a diagnosis of IPAH, 52.8% of those with other diagnoses (collagen tissue disease, rare cases (venoocclusive disease, portal hypertension)), 33.6% of those with a congenital diagnosis, 77.6% of those with a diagnosis of CTEPH, 88.9% of the disproportionate ones are in the '50 and over' age group. A statistically significant difference was found between the distribution of the number of medications used according to the diagnoses ($p<0.001$). This difference is due to the fact that the ratios of the number of medications used differ according to the diagnoses. 77.8% of those with a diagnosis of IPAH, 76.7% of those with (collagen tissue disease, rare cases), 55.6% of those with a congenital diagnosis, 87.5% of those with a diagnosis of CTEPH, and 100% of those with disproportionate use of only one medication. A statistically significant difference was found between the distribution of medication use according to diagnoses ($p<0.001$). 97.8% of those with IPAH, 83.3% of those with (collagen tissue disease, rare cases 98.2% of those with a congenital diagnosis, 75.3% of those with a diagnosis of CTEPH, and 98.1% of those with disproportionate PAH use medications. A statistically significant difference was found between the distribution of functional classes according to diagnoses ($p<0.001$). This difference is due to the difference in the rates of class I, II and III according to diagnoses. 53.3% of those with IPAH diagnosis, 36.1% of those with (collagen tissue disease, rare cases), 62.4% of those with congenital diagnosis, 64.7% of those with CTEPH, 48.1% of those with

disproportionate are in class II, while 37.8% of patients those diagnosed with IPAH, 22.2% of those with (collagen tissue disease, rare cases), 18.3% of those diagnosed with congenital, 31.8% of those diagnosed with CTEPH, 44.4% of which is disproportionate are in class III. When comparing the quantitative data according to the diagnoses (table 5), a statistically significant difference was found between the median age values of the patients ($p<0.001$). The median age of the diagnosis of IPAH was 60.5, the median age of those with (collagen tissue disease, rare cases) was 50.5, the median age of those with congenital diagnosis was 38.0, the median of the diagnosis of CTEPH was 65.0 and the median of the diagnosis of disproportionate pulmonary hypertension was 66.0. This difference is due to the fact that the median age of those with IPAH was higher than the median age of the congenital diagnosis, and the median of CTEPH and disproportionate diagnoses was higher than the median of congenital and other diagnoses. A statistically significant difference was found between the median sPAB values according to the diagnoses ($p<0.001$). The median sPAB of the diagnosis of IPAH was 75.0, the median of sPAB of those with (collagen tissue disease, rare cases)was 44.0, the median of sPAB of those with congenital diagnosis was 78.5, the median sBAP of diagnosis of CTEPH was 80.0, and the median sPAB of disproportionate diagnosis was 78.0. **"**This difference is due to the fact that those with a diagnosis of IPAH are numerically lower than other diseases that cause PH"

When the quantitative data were compared according to the survival status (table 6), a statistically significant difference was found between the median age of the patients according to the survival status ($p=0.020$). While the median age of those who were alive was 56.0, the median age of those who were dead was 66.0. A statistically significant difference was found between the mean sPAB values according to survival status ($p=0.004$). While the average of the living ones was 73.7, the average of the dead ones was 84.4. A statistically significant difference was found between the median values of the follow-up period according to the survival status ($p=0.002$). While the median of the living was 36.0 months, the median of the dead ones was 26.0 months.

When categorical variables were compared according to survival status (table 7), a statistically significant difference was found between the distributions of gender ($p=0.035$). While 71.2% of those who survived were women, 56.6% of those who died were women. A statistically significant difference was found between the distribution of the number of medications used according to survival status ($p=0.032$). While 6.3% of those who were alive use 3 medications, 17.8% of those who died use 3 medications. A statistically significant difference was found between the distribution of functional class according to survival status ($p<0.001$). This difference is due to the fact that the rates of each class differ according to their survival status. While 0.4% of those who are alive are in class IV, 24.5% of those who are dead are in class IV. A statistically significant difference was found between the distribution of diagnosis dates according to survival status ($p=0.004$).

When the survival time was compared according to the categorical variables (Table 8), a statistically significant difference was found between the mean survival time by gender ($p=0.025$). While the average survival rate for women was 100.4 months, the mean for men was 84.5months. A statistically significant difference was found between the mean survival time according to the diagnoses ($p=0.005$). This difference is due to the fact that the mean survival time for congenital diagnosis is higher than the mean survival time for IPAH, CTEPH and disproportionate diagnoses. A statistically significant difference was found between the mean survival time values according to medication use ($p=0.014$). While the mean survival time of the non-medication group was 62.6 months, the mean survival time of the medication users was 99.1 months. A statistically significant difference was found between the mean survival time according to functional classes ($p<0.001$). The mean survival time of Class I was 99.7 months, the mean of survival of II was 90, the mean of III was 78.5, and the mean of IV was 53.0. The independent risk factors affecting the survival time were analyzed by COX regression analysis as Univariate and Multivariate models (Table 9). When univariate results are examined, the mortality risk increases 1.021 times as age increases. The mortality risk of men is 1.863 times higher than women. The mortality risk of those with a congenital diagnosis is 0.36 times less than those with a diagnosis of IPAH. The mortality risk is 0.398 times lower in medication users. The mortality risk is 11,607 times higher for those who are in class III compared to those who are in functional class I, and 26.486 times higher than those who are in class IV. The risk of mortality increases 1.016 times as the spab increases. According to the results of the multivariate model, the mortality risk increases 1.022 times as the age increases. The mortality risk of men is 2,551 times higher than that of women. The mortality risk of those with congenital diagnosis is 0.278 times less than those with a diagnosis of IPAH. Those who use three drugs have a 3,073 times higher risk of mortality than those who use one drug. Mortality risk increases 1.022 times as sPAB increases.

Table 1: Pulmonary Hypertension Classification (2018) [2]

1- Pulmonary arterial hypertension (PAH) 1.1 Idiopathic 1.2 Hereditary 1.3 Due to drugs and toxins 1.4 Associated with other diseases 1.4.1 Connective tissue diseases 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1.5 PAH with response to long-term CCB 1.6 PAH with venous/capillary findings (PVOD/PKH) 1.7 Persistent pulmonary hypertension of the newborn	**3-PH due to lung diseases and/or hypoxia** 3.1 Obstructive lung disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases of mixed restrictive and obstructive nature 3.4 Hypoxia (without lung disease) 3.5 Developmental abnormalities **4- Chronic thromboembolic PH and other pulmonary artery obstructions** 4.1 Chronic thromboembolic pulmonary hypertension 4.2 Other pulmonary artery obstructions
2- PH due to left heart disease 2.1 PH due to heart failure with preserved EF 2.2 PH due to heart failure with decreased EF 2.3 Valve disease 2.4 Congenital/acquired cardiovascular conditions causing postcapillary PH	**5- PH with uncertain mechanisms and/or multifactorial** 5.1 Hematological disorders 5.2 Systemic disorders and metabolic diseases 5.3 Others: 5.4 Complex congenital heart diseases

Table 2: Recommendations for pulmonary hypertension referral center [2, 6, 7]

Recommendation	Recommendation Class	Level of Evidence
Referral centers should work as a multiprofessional team. (cardiologists and respiratory diseases specialists (normally one or both cardiology and respiratory diseases specialists), clinical specialist nurses, radiologists, psychologists and social counseling, answering phone calls)	I	C
Referral centers should have direct vonnections with other services (eg, connective tissue diseases service, family planning service, lung transplantation service, adult congenital heart disease service) and have rapid referral facilities.	I	C
A PAH center should monitor 50 patients with PAH or CTEPH, and referral to the center for new documented patients with at least 2 documented PAHs or CTEPH per month.	IIa	C
At least 20 vasoreactivity tests per year should be performed in referral centers	IIa	C
Referral centers should participate in common clinical trials for PAH, including intermediate phase II and Phase III clinical trials.	IIa	C

Table 3: Descriptive statistics of quantitative data

	Mean	Standard deviation	Median	Minimum	Maximum
Age	54,6	18,4	56,0	15,0	95,0
Systolic pulmonary artery pressure (sPAB)	75,4	24,7	75,0	29,0	160,0
Follow-up time/month	44,9	27,3	36,0	2,0	120,0

Table 4: Frequency distribution of categorical data

	Frequency (n)	Percent (%)
Age group		
<50	122	36,9
50 and above	209	63,1
Gender		
Woman	228	68,9
Man	103	31,1
Diagnosis		
Rare cases (pulmonary veno-occlusive disease (PVOD),portal hipertansiyon(PoHT))	6	1,8
Idiopathic pulmonary arterial hypertension (IPAH)	46	13,9
Collagen tissue disease (CTD)	30	9,1
Congenital heart disease (CHD)	110	33,2
Chronic thromboembolic pulmonary hypertension (CTEPH)	85	25,7
Disproportionate Pulmonary Hypertension (DPH)	54	16,3

Number of medications used		
one	227	75,7
two	49	16,3
three	24	8
Medication Use		
Yes	300	90,6
No	31	9,4
Survival		
Alive	278	84,0
Dead	53	16,0
Functional class (WHO-FC)		
I	33	10,0
II	186	56,5
III	96	29,2
IV	14	4,3
Medication*		
Endothelin receptor antagonist	140	42,3
Calcium channel blocker	96	29
Phosphodiesterase enzyme 5 inhibitor	58	17,5
Riociguat	53	16
Prostacyclin analog	48	14,5
Refuse to use medication	32	9,7
Tadalafil	1	0,3

Table 5: Comparison of categorical data according to diagnoses

	IPAH	**Other (CTD,PVOD, PoHT)**	**Congenital**	**CTEPH**	**Disproportionate**	**Total**	**Test statistic**	**p**
Age group								
<50	7 (15,2)a	17 (47,2)bc	73 (66,4)c	19 (22,4)ab	6 (11,1)a	122 (36,9)	χ^2=75,132	**<0,001**
50 and above	39 (84,8)	19 (52,8)	37 (33,6)	66 (77,6)	48 (88,9)	209 (63,1)		
Gender								
Woman	38 (82,6)	29 (80,6)	71 (64,5)	54 (63,5)	36 (66,7)	228 (68,9)	χ^2=8,557	0,073
Man	8 (17,4)	7 (19,4)	39 (35,5)	31 (36,5)	18 (33,3)	103 (31,1)		
Number of medications used								
One	35 (77,8)ab	23 (76,7)ab	60 (55,6)b	56 (87,5)ac	53 (100)c	227 (75,7)	χ^2=48,372	**<0,001**
Two	8 (17,8)a	4 (13,3)ab	30 (27,8)a	7 (10,9)ab	0 (0)b	49 (16,3)		
Three	2 (4,4)ab	3 (10)ab	18 (16,7)b	1 (1,6)a	0 (0)a	24 (8)		
Medication Use								
No	1 (2,2)ab	6 (16,7)bc	2 (1,8)a	21 (24,7)c	1 (1,9)ab	31 (9,4)	χ^2=39,601	**<0,001**
Yes	45 (97,8)	30 (83,3)	108 (98,2)	64 (75,3)	53 (98,1)	300 (90,6)		
Survival								
Alive	37 (80,4)	32 (88,9)	99 (90)	65 (76,5)	45 (83,3)	278 (84)	χ^2=7,620	0,107
Dead	9 (19,6)	4 (11,1)	11 (10)	20 (23,5)	9 (16,7)	53 (16)		
Functional class (WHO_FS)								
I	3 (6,7)ab	14 (38,9)c	14 (12,8)b	1 (1,2)a	1 (1,9)ab	33 (10)	χ^2=59,964	**<0,001**
II	24 (53,3)ab	13 (36,1)b	68 (62,4)ab	55 (64,7)a	26 (48,1)ab	186 (56,5)		
III	17 (37,8)ab	8 (22,2)ab	20 (18,3)b	27 (31,8)ab	24 (44,4)a	96 (29,2)		
IV	1 (2,2)	1 (2,8)	7 (6,4)	2 (2,4)	3 (5,6)	14 (4,3)		

χ^2: Chi-square test statistic, a-c: No difference between diagnoses with the same letter in each condition

Table 6: Comparison of quantitative data according to diagnoses

	IPAH	**Other (CTD,PVOD, PoHT)**	**Congenital**	**CETPH**	**Disproportionate**	**Test statistic**	**p**
Age	59,8 ± 13,0	52,2 ± 13,4	42,3 ± 18,2	62,6 ± 16,5	64,6 ± 13,7	χ^2=79,258	**<0,001**
	60,5 (18,0 - 84,0)ac	50,5 (21,0 - 82,0)bc	38,0 (15,0 - 86,0)b	65,0 (15,0 - 91,0)a	66,0 (21,0 - 95,0)a		
sPAB	77,4 ± 23,7	54,5 ± 25,4	78,8 ± 28,1	79,0 ± 20,1	74,9 ± 17,0	χ^2=27,639	**<0,001**
	75,0 (35,0 - 160,0)b	44,0 (29,0 - 120,0)a	78,5 (30,0 - 155,0)b	80,0 (40,0 - 130,0)b	78,0 (42,0 - 115,0)b		
Follow-up time/month	40,1 ± 25,1	47,4 ± 24,0	52,7 ± 29,1	34,1 ± 27,1	48,3 ± 21,4	χ^2=26,87	**<0,001**
	36,0 (4,0 - 120,0)ab	36,0 (15,0 - 120,0)ab	44,5 (6,0 - 120,0)b	36,0 (2,0 - 120,0)a	48,0 (12,0 - 96,0)b		

χ^2: Kruskal Wallis test statistic, a-c: No difference between diagnoses with the same letter, mean ± s. deviation, median (minimum – maximum)

Table 7: Comparison of quantitative data by survival status

	Alive		**Ex**		**Test statistic**	**p**
	Mean. ± s deviation	**Mean. (min. - max.)**	**Mean. ± p. deflection**	**Mean. (min. - max.)**		
Age	53,8 ± 17,7	56,0 (15,0 - 95,0)	59,1 ± 21,2	66,0 (15,0 - 87,0)	U=5884,5	**0,020**
sPAB	73,7 ± 24,7	73,5 (29,0 - 160,0)	84,4 ± 22,9	87,0 (30,0 - 130,0)	t=-2,919	**0,004**
Follow-up time/month	46,6 ± 26,6	36,0 (6,0 - 120,0)	35,8 ± 29,3	26,0 (2,0 - 120,0)	U=5307,5	**0,002**

t: Two independent samples t-test statistic, U: Mann-Whitney U test statistic

Table 8: Comparison of categorical variables by survival status

	Alive	**Ex**	**Total**	**Test statistic**	**p**
age group					
<50	104 (37,4)	18 (34)	122 (36,9)	χ^2=0,227	0,633
50 and above	174 (62,6)	35 (66)	209 (63,1)		
Gender					
Woman	198 (71,2)	30 (56,6)	228 (68,9)	χ^2=4,438	**0,035**
Man	80 (28,8)	23 (43,4)	103 (31,1)		
Number of medications used					
One	197 (77,3)	30 (66,7)	227 (75,7)	χ^2=6,913	**0,032**
Two	42 (16,5)	7 (15,6)	49 (16,3)		
Three	16 (6,3)[a]	8 (17,8)[b]	24 (8)		
Medications use					
No	23 (8,3)	8 (15,1)	31 (9,4)	χ^2=2,440	0,118
Yes	255 (91,7)	45 (84,9)	300 (90,6)		
Nyha (functional class)					
I	32 (11,6)a	1 (1,9)b	33 (10)	χ^2=111,741	**<0,001**
II	180 (65,2)a	6 (11,3)b	186 (56,5)		
III	63 (22,8)a	33 (62,3)b	96 (29,2)		
IV	1 (0,4)a	13 (24,5)b	14 (4,3)		

χ^2: Chi-square test statistic, aB: No difference between diagnoses with the same letter in each case

Table 9: Comparison of survival time according to categorical variables

	Mean survival time (95% CI)	**p [1]**
age group		
<50	100,2 (91,4 - 109,0)	0,214
50 and above	96,7 (89,6 - 103,9)	
Gender		
Woman	100,4 (93,6 - 107,2)	**0,025**
Man	84,5 (75,9 - 93,0)	
Diagnosis		
IPAH	91,5 (75,0 - 108,1)a	**0,005**
Other (CTD,PVOD, PoHT)	98,8 (80,1 - 117,6)ab	
Congenital	106,9 (99,1 - 114,7)b	
CETPH	88,4 (76,1 - 100,7)a	
Disproportionate	83,8 (75,7 - 91,9)a	
Number of medications used		
one	99,2 (91,9 - 106,6)	0,4

Two	103,8 (92,8 - 114,9)	
Three	91,5 (74,3 - 108,7)	
medication use		
No	62,6 (50,2 - 74,9)	**0,014**
Yes	99,1 (93,3 - 104,9)	
WHO/NYHA(functional class)		
I	99,7 (95,3 - 104,1)c	**<0,001**
II	116,0 (112,4 - 119,5)c	
III	78,5 (67,8 - 89,2)b	
IV	53,0 (32,9 - 73,1)a	

[1] Log Rank (Mantel-Cox) test, a-c: No difference between groups with the same letter

Table 10: Functional classification of pulmonary hypertension according to the New York Heart Association (NYHA) and the World Health Organization (WHO)

Class	Symptom/functions
NYHA/WHO I	No restriction of effort in usual daily physical activity
NYHA/WHO II	Mild dyspnea, fatigue, or chest pain present with usual daily physical activity
NYHA/WHO III	Significant limitation of effort with mild physical activities, dyspnea, fatigue, or chest pain
NYHA/ WHO IV	The patient is symptomatic in all kinds of physical activities, even in the resting position, dyspnea and or fatigue, and the presence of signs of right heart failure

Table 11: Cox regression analysis results

	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Age	1,021 (1,006 - 1,037)	**0,008**	1,022 (1,001 - 1,043)	**0,036**
Age group	1,443 (0,806 - 2,583)	0,217		
Gender-male	1,863 (1,069 - 3,245)	**0,028**	2,551 (1,327 - 4,905)	**0,005**
Diagnosis (IPAH)				
Other (CTD,PVOD, PoHT)	0,477 (0,147 - 1,549)	0,218	0,485 (0,128 - 1,838)	0,287
Congenital	0,36 (0,148 - 0,875)	**0,024**	0,278 (0,098 - 0,79)	**0,016**
CETPH	1,345 (0,608 - 2,977)	0,464	0,74 (0,302 - 1,814)	0,511
Disproportionate	0,737 (0,292 - 1,863)	0,519	0,59 (0,221 - 1,574)	0,292
Number of medications used (1)				
Number of medications used - 2	0,817 (0,355 - 1,883)	0,635	1,208 (0,48 - 3,041)	0,688
Number of medications used - 3	1,559 (0,701 - 3,467)	0,277	3,073 (1,188 - 7,953)	**0,021**
Medication use (None)	0,398 (0,186 - 0,852)	**0,018**		
WHO/Nyha (functional class I)				
II	0,896 (0,105 - 7,673)	0,920		
III	11,607 (1,585 - 85,013)	**0,016**		
IV	26,486 (3,444 - 203,685)	**0,002**		
sPAB	1,016 (1,005 - 1,028)	**0,004**	1,022 (1,007 - 1,037)	**0,004**

*(reference category), Enter method was used to include independent risk factors in the model

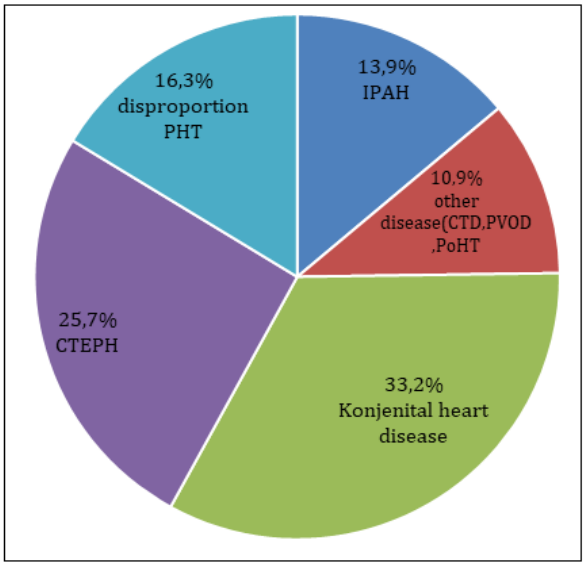

Figure 1: Pie chart of diagnoses

DISCUSSION

Pulmonary hypertension (PH) is a chronic and progressive cardiopulmonary disease. The pathophysiology of pulmonary hypertension, which was previously defined as primary and secondary, was largely clarified over time, and the first modern classification, diagnosis and treatment guideline was created in 1998 [6]. Then 2003, 2008, 2013, 2018 guidelines were created and the classification was updated each time. There is no clear data epidemiologically including the incidence of all PH groups, thus reflecting the true prevalence of PH in the community.

Since the initial accumulation of data in the 1980s, subsequent registry databases have provided information on patients' demographic factors, treatment, and survival, and have allowed comparisons between populations in different periods and environment.

Registry studies on epidemiological data were first established by the National Institute of Health (NIH) in the United States. Only IPAH patients were evaluated here [2, 8]. Over time, registration studies of other countries including more patient numbers were formed. So far, there have been common registration studies in which many countries have participated, as well as local registration studies. There are more than 7000 recording studies. In the years when pulmonary hypertension was first defined, USNIH (1981-1985) (187 patients in 32 centers), USPHC (1982-2006) (3 centers 578 patients) Scottis morbidity record (SMR)(1986-2001) (374 patients), french registry (2002-2003)(17 centers, 674 patients), chinese (1999-2004) (single center 72 patients), spanish(1998-2008) (31 centers, 1028 patients), UK (2001-2009) (8 centers, 482) Registry studies such as the Mayo clinic (1998-2004) (single center 484 patients), and the New Chinese Registry (9 centers 96 patients) led to these studies [9]. Other international registry studies created in the following years (US REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) (2008-2009) (55 centers 3515 patients), COMPERA (Comparative, Prospective Registry of New Initiated Therapies for Pulmonary Hypertension) (2007-2018) (31 centers, 8200 patients) created large registry data on patient characteristics, and with these data, populations were characterized, disease burden was evaluated, and risk classification tools were developed (9). There are many registry studies on pulmonary arterial hypertension. Our data, which is formed as a single center, will contribute to these registration studies.When all registry studies were evaluated, the number of patients we reported as a center was high. This situation may be related to the geography we live in. When the studies are evaluated in detail, it may be related to the higher number of some subgroups such as congenital diseases.

Group 1 PAH patients constituted the majority of the cases in the registry studies, which included patients who were referred to reference centers with the suspicion of pulmonary hypertension and were referred to reference centers for RHC [10]. In two important registry studies reported from our country, it is observed that 61-69% of the cases were composed of Group 1 PAH cases, and Group 4 CTEPH cases were the second most common [11, 12]. In these studies, idiopathic PAH (IPAH) is the most common cause of Group 1 PAH, and PAH cases associated with connective tissue disease appear to be in the second place [9, 12]. In our data, the most common disease in group 1 is congenital heart disease, followed by IPAH, collagen tissue disease has been observed. It can be said that the reason why congenital heart diseases are common is the low socio-cultural level of the place where we live and these patients are late patients who were not treated in childhood. Although there are differences between countries in congenital heart diseases, it can be said that the rate of PAH development in ASD is 10% and the rate of PAH development in VSD is 20% [6]. It is a fact that the incidence of PAH will gradually decrease if early diagnosis and interventional intervention are done quickly. After the development of Eisenmenger syndrome, the development of pulmonary hypertension is inevitable and irreversible.

In our data, the most common disease group is congenital heart disease, followed by CTEPH and IPAH, collagen tissue disease, and disproportionate pulmonary hypertension have been observed.The frequency of CTEPH patients is increasing day by day. This may be due to the increase in awareness and the high number of embolism patients seen in our region. The absence of HIV, and to be out numbered of portopulmonary hepatitis, and veno-occlusive patients may be due to the restrictions on departments not referring to these patients.

Group 2 and group 3 patients included patients with pulmonary hypertension associated with their own diseases. Among these groups, pulmonary hypertension patients, which were previously defined as disproportionate, are still followed in PAH centers [7]. Patients with disproportionate pulmonary hypertension are not included in many registries. This is among the limitations of recording studies. In the registry studies of the thoracic society and cardiology associations in Turkey, this rate was reported as 12-14% in group 2 and group 3. In our data, this rate was found to be 16.3%. Whether this is disproportionate pulmonary hypertension or the large number of IPAH comorbid patients remains a matter of debate.

In general, female gender constitutes 64-80% of the cases in all PAH registry studies. Although the mean age varies according to the diagnosis groups, it varies between 36 and 65 years [13, 9]. When we look at our data, it was determined that 68.9% of the patients were female, with an average age of 54.6%, and 63% of the patients were over 50 years old. It was observed that these values were similar to the recording studies.

In the US National Institute of Health (NIH) study, in which only IPAH patients were evaluated 2.8, it was found that the f/e ratio was 1.7, the mean age was 36.4, and there was no difference about ethnic origin or gender. In order to distinguish between ethnic origins, a multicenter study is required.

In the French registry series, the F/E ratio was 1.9 and the mean age was 50±15 years [14]. In the reveal series, the mean age was found to be 53.6+16 years. According to the first registration study in the USA, it was observed that the ratio of women to men increased to 4.1 [15]. It is clear that the most important factor affecting the frequency of PAH periodically is the PAH group associated with appetite suppressants. It is clear that the incidence, gender and average age will

change in the registry studies conducted within a 2-year period, which included the release of the medication called aminorex fumarate, which is an appetite suppressant, and its withdrawal [6, 16].

Some mutations have been reported in patients defined as the hereditary group in group 1 pah patients. Like the BMPR2 mutation and the ALK-1 … mutation. The characteristics of acute vasodilator response and response to calcium channel blockers in patients with these mutations have been suggested. It is known that these mutations occur in 50-90% of PAH patients [17]. It is known that the survival of patients with mutations will also change. In case of mutation, patients may need to be evaluated early in terms of combination treatments and transplantation. However, we have a deficit in genetic counseling in our PAH center, so unfortunately, genetic examination is not routinely performed in our patients.

Collagen tissue diseases in group 1 were found to be 16.3% in our study. It has been reported connective tissue diseases were 25.9% in the reveal series, 15.3% in the french registry series, and 22% in the thoracic society registry study [12, 14, 18]. It is clear that scleroderma is the group most commonly found to have PAH in these studies. In our study, the rate of scleroderma was found to be the most common as 5.9%. Afterwards, Behçet's disease and SLE were detected, respectively. Lack of referral of connective tissue patients to PAH centers may be changing our patient rates.

When the registry studies in recent years were reviewed, the results of the 6-minute walk test and right heart catheterization were evaluated in some registry studies and it was reported that these results supported the diagnosis of PAH. Most of these studies are prospective studies. Our study was arranged retrospectively, and patients had multiple tests which are right heart catheterizations, 6-minute walk tests, and BNP values, mainly at the time of diagnosis and during follow-up. These were not specified in the study. This may be a limitation of our study. These can be used as data for another study. When the functional class of the patients at the time of first admission were examined, 53.3% of those with IPAH diagnosis, 36.1% of those with (collagen tissue disease, rare cases), 62.4% of those with congenital diagnosis, 64.7% of those with CTEPH, and 48.1% of those with disproportionate were Class II, while 37.8 % of those with a diagnosis of Ipah, 22.2% of those with other diagnoses, 18.3% of those with a congenital diagnosis, and 31.8% of those with a diagnosis of CTEPH were Class III. When other registry studies were examined, it was observed that 55-91% of all patient groups were class III and IV (9). The high rate of functional class II patients among the patients followed in our study may be due to the higher number of congenital heart patients and CTEPH patients with better prognosis compared to other studies.

Pulmonary arterial hypertension (PAH) remains a serious clinical condition despite the use of multiple medications targeting the endothelin, nitric oxide and prostacyclin pathways in the last 15 years. The current treatment algorithm determines the most appropriate initial strategy, including monotherapy or double or triple combination therapy. Treatment may need to be increased further if a low-risk status is not achieved according to a planned follow-up strategy. Despite maximal medical treatment, lung transplantation may be required in the most advanced cases. The 2015 ESC/ERS PH guidelines tables recognize that the treatment approach and treatment options for PAH in various hospitals and clinical settings may vary depending on local accessibility (and profession) (7).Only 4 of our patients are currently undergoing lung transplantation, and 2 of them are being followed as patients with disproportionate pulmonary hypertension and 2 of them are being followed as patients with pulmonary veno-occlusive disease (PVOD). The fact that the conditions such as living in the city where the transplant center is located cannot be met may explain the low number of transplant patients.

When the medication use status of the patients was evaluated, 77.8% of those with IPAH diagnosis, 76.7% of those with other diagnoses, 55.6% of those with congenital diagnosis, 87.5% of those with CTEPH, and 100% of those with disproportionate diagnosis uses only one medication. A statistically significant difference was found between the distribution of medication use according to diagnoses ($p<0.001$). There are some patient groups for which a single drug is recommended: For example;

- PAH patients associated with HIV infection, portal hypertension, or uncorrected congenital heart disease, as they were not included in retrospective registry studies that tried initial combination therapy
- Functional class 2 patients followed for a long time with a single treatment
- IPAH patients over 75 years of age with multiple risk factors (high blood pressure, diabetes mellitus, coronary artery disease, atrial fibrillation, obesity) for heart failure with preserved left ventricular ejection fraction can be given monotherapy [19].

The possible reasons for the high rate of taking a single drug in our patients are; the high number of congenital heart patients, the high number of patients that we have followed for a long time as a center with a low functional class with a single drug, and the fact that we have disproportionate pulmonary hypertension patients with IPAH.

In order to create healthy survival analyzes in these patient groups, prospectively planned studies should be conducted with a large number of patients, including each of the PAH patient groups and all confounding factors (age, gender, disease duration, comorbidities, medications used, functional class, 6 min walk test, right heart catheterization results, echocardiographic data, symptoms, etc.) should be analyzed. For this, randomized controlled studies are needed. There are retrospective analyzes in the literature, as in our study. The high number of patients can give an idea about survival and we decided to present our data with the thought that it could be a preliminary study. The independent risk factors affecting the survival time were determined as advanced age, male gender, IPAH patient group, medication use, high systolic pulmonary artery pressure value, and high functional class. World Health Organization functional classes (WHO-FC) (Table 11) remain a strong predictor of survival, although there is great variability between measurements made by different individuals. Old data for patients with untreated IPAH or hereditary PAH show that median survival is 6 months in WHO-FC IV, 2.5 years in WHO-FC III, and 6 years in WHO-FC I and II [6]. When we look at our study data, we saw that the survival decreased as the functional class increased in correlation with this information. In addition to this result, we observed that survival was better in our congenital heart patients.

3-year survival rates are 35% in untreated IPAH compared to 77% in patients with Eisenmenger syndrome [6]. These data, in line with our data, showed that the survival of patients with congenital heart diseases was better.

When our data were evaluated, we observed that survival was better in CTD (connective tissue diseases) compared to IPAH. However, one study showed that connective tissue patients had a shorter survival compared to IPAH (6). The fact that the majority of the connective tissue patients we followed up had scleroderma and the longer life expectancy of these patients may explain this situation.

In our study, although female gender predominance and advanced age were observed in accordance with the literature, it was observed that survival is worse in male gender. Although it is different in patient groups, for example, death is higher in the female gender in connective tissue diseases [6].

There are many studies showing that single, double or triple therapies improve survival [7]. Combination therapy with accepted PAH medications is recommended for patients who do not respond adequately to monotherapy, but combination therapy should be applied only in specialized centers. Whether the response to monotherapy is adequate or not can only be decided on an individual basis.

Such a decision will be based on an inadequate clinical response in a particular patient despite monotherapy and the optimal level of previous therapy. It is known that PAH-specific medications affect survival [7]. When our data is evaluated, although it was observed that the survival of those who took triple medications was worse, it would be normal to explain this by the poor functional classes of the patients, not the medications used.

CONCLUSION

"Pulmonary hypertension is a disease with high mortality and includes different disease groups". The follow-up of these patients in PAH centers and the use of special medications affect mortality rates. There are many registry studies on pulmonary arterial hypertension. Our data, which is formed as a single center, will contribute to these registration studies.

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