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Long-Term Natural Course of Patients with Pulmonary Artery Pressures in the Range of 21–24 mmHg: Insights from a Single-Center Study

Pulmoner Arter Basınçları 21–24 mmHg Aralığında Olan Hastaların Uzun Vadeli Doğal Seyri: Tek Merkez Deneyimi

ABSTRACT

Objective: Slightly elevated mean pulmonary artery pressure (mPAP) was previously termed as "borderline pulmonary hypertension (PH)". We examined the long-term prognosis of patients with mPAP values between 21 and 24 mmHg, who were referred with the suspicion of pulmonary hypertension.

Methods: Our retrospective study included patients with moderate-to-high echocardiographic risk who underwent right heart catheterization (RHC) between 2008 and 2021 and were followed for at least 1 year. Patients with mPAP <21 mmHg and mPAP 21–24 mmHg were compared. Demographic and clinical characteristics and prognoses of the groups were compared. All-cause mortality over a mean follow-up of 5 years (min 1–max 13 years) was evaluated.

Results: A total of 140 patients (mean age 53.1 ± 14.8 years, female 74.5%) with mPAP values <25 mmHg measured of the 395 diagnostic RHCs. Mean follow-up was 4.92 ± 3.13 years. NT-pro-BNP and 6-min walking distance were better in patients with mPAP <21 mmHg. Echocardiographic findings suggestive of PH were more common in mPAP 21–24 mmHg group ($P < 0.05$). Both the pulmonary artery wedge pressure and cardiac index values were significantly deteriorated in individuals with mPAP 21–24 mmHg ($P = 0.001$). All-cause mortality tended to be higher in the borderline PH group but did not reach to statistical significance.

Conclusion: Our single-center observational study revealed that the individuals with an mPAP of 21–24 mmHg tended to have a worser prognosis than those with mPAP of <21 mmHg for up to 13-year follow-up.

Keywords: Invasive hemodynamics, pulmonary artery pressure, pulmonary hypertension, right heart catheterization, survival

ÖZET

Amaç: İstirahat halinde hafifçe yükselmiş ortalama pulmoner arter basıncı (oPAB) daha önce "sınırda pulmoner hipertansiyon (PH)" olarak adlandırılıyordu. Çalışmamızda bu amaçla pulmoner hipertansiyon şüphesi ile sevk edilen oPAB değerleri 21–24 mmHg arasında olan hastaların uzun dönem prognozunu inceledik.

Yöntem: Retrospektif çalışmamıza, 2008–2021 yılları arasında sağ kalp kateterizasyonu (SKK) uygulanan ve en az 1 yıllık takip kriterlerini karşılayan, orta ila yüksek ekokardiyografik riske sahip hastaları içermektedir. oPAB <21 mmHg ve oPAB 21–24 mmHg olan hastalar karşılaştırıldı. Grupların demografik ve klinik özellikleri ile prognozları karşılaştırıldı. Ortalama 5 yıllık (en az 1-en fazla 13 yıl) takip boyunca tüm nedenlere bağlı ölümler değerlendirildi.

Bulgular: 395 tanısal SSK'dan oPAB değerleri <25 mmHg olan toplam 140 hasta (ortalama yaş 53.1 ± 14.8 yıl, kadın 74.5%) değerlendirmeye alındı. Ortalama takip süresi 4.92 ± 3.13 yıldı. NT-pro-BNP ve 6 dakikalık yürüme mesafesi oPAB <21 mmHg olan hastalarda daha iyiydi. PH düşündüren ekokardiyografik bulgular oPAB 21–24 mmHg grubunda daha sıktı ($P < 0.05$). oPAB 21–24 mmHg olan bireylerde hem pulmoner arter kama basıncı yüksekti hem de kardiyak indeks değerleri anlamlı olarak daha düşüktü ($P = 0.001$). Tüm nedenlere bağlı ölüm, sınırda PH grubunda daha yüksek olma eğilimindeydi ancak istatistiksel anlamlılığa ulaşmadı.

Sonuç: Tek merkezli gözlemsel çalışmamız, 13 yıla kadar takipte oPAB değeri 21–24 mmHg olan bireylerin prognozunun oPAB <21 mmHg olanlara göre daha kötü olma eğilimde olduğunu ortaya koydu.

Anahtar Kelimeler: İnvaziv hemodinami, pulmoner arter basıncı, pulmoner hipertansiyon, sağ kalp kateterizasyonu, prognoz

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Burcu Yağmur
Meral Kayıkçıoğlu
Evrim Şimşek
Sanem Nalbantgil
Hakan Kültürsay

Department of Cardiology, Ege University Faculty of Medicine, İzmir, Türkiye

Corresponding author:
Burcu Yağmur
✉ burcu.yagmur@ege.edu.tr

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The definition of pulmonary hypertension (PH) is primarily based on hemodynamic assessment of mean pulmonary artery pressure (mPAP) using the right heart catheterization (RHC). Under physiological conditions, normal mPAP is 14.0±3.3 mmHg (mean ± SD).[1] The prognostic significance of slightly elevated mPAP, previously termed as "borderline PH," is a matter of debate. There have been changes regarding lower the cutoff or threshold values for the diagnosis of PH using mPAP in the latest guidelines. One of the key recommendations from the sixth World Symposium on PH (WSPH) was to revise the hemodynamic definition of PH.[2] New definition of PH has been added and expanded to the current PH guidelines, including a revised threshold level for pulmonary vascular resistance (PVR) based on the expert reviews. According to the recent guidelines, PH is defined as a resting mPAP >20 mmHg.[3] Based on available data, the upper limit of normal PVR has also been revised to 2 Wood units (WU), which represents the lowest threshold for PVR with prognostic relevance. However, some clinicians and researchers are still not convinced about this lower threshold levels and there are doubts and uncertainties. Studies suggest that even slightly elevated mPAP values in the range of 18–25 mmHg may have prognostic significance.[4] However, the long-term natural history of borderline PH is still not well addressed.

In addition to the changing definition of PH, further studies are needed to determine the treatment requirements of patients with mPAP values in the 20–25 mmHg range, considering that the current limit for the pulmonary arterial hypertension (PAH)-specific treatment is still mPAP ≥25 mmHg as determined by randomized studies. We evaluated the clinical data and long-term prognosis of patients with mPAP values in the range of 20<–<25 mmHg, who underwent RHC with a suspected PH. We also aimed to determine how many of these patients would ultimately receive a definite diagnosis of PAH during long-term follow-up.

Materials and Methods

This retrospective and cohort study was conducted at Ege University Medical School Cardiology Department (PH Center).

ABBREVIATIONS

6MWD	6-min walking distance
CI	Cardiac index
CO	Cardiac output
CongHD	Congenital heart disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CV	Cardiovascular
LVEF	Left ventricular ejection fraction
mPAP	Mean pulmonary artery pressure
NT-proBNP	n-terminal pro-B-type natriuretic peptide
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RAA	Right atrial area
RAP	Right atrial pressure
RHC	Right heart catheterization
RVEF	Right ventricular ejection fraction
TAPSE/sPAP	Tricuspid annular plane systolic excursion/ systolic pulmonary artery pressure
TRV	Tricuspid regurgitation velocity
WHO-FC	World Health Organization-functional class

The study included all patients who were aged 18 years or older and had a minimum of 1 year of follow-up after the diagnostic RHC for suspected PH from 2008 to 2021. In addition, patients with pulmonary stenosis, mild-severe aortic stenosis, constrictive pericarditis, and heart transplant candidates were excluded from the study. All patients were treatment naïve for pulmonary dilatator therapies and we categorized the study population into groups according to their preliminary diagnoses similar to the PH grouping. The decision to perform RHC and the subsequent diagnosis was made in accordance with the present PH guidelines. The study protocol was approved by the Ege University Review Board (Approval Number: E.226136, Date: 13.07.2021).

Patients were categorized based on the mPAP values obtained from the RHC reports. A comparison was made between patients with mPAP values of 20 mmHg and below (within normal limits) and those with mPAP values in the range of 21–24 mmHg. Analysis covered the demographic characteristics, clinical features, and prognoses of the patient groups. Patients were included in the analysis if data were available from mPAP, pulmonary artery wedge pressure (PAWP), cardiac output (CO) measured by eFick methods, and a full RHC report conducted in our center. In patients with repeated RHCs, only the first RCH was included in the analysis. All enrolled patients had at least 1-year follow-up data available for outcomes. Our primary outcome of interest was all-cause mortality after adjusting for clinically relevant covariates in a Cox proportional hazards model.

PH was diagnosed based on a mPAP of 25 mmHg or above measured during the RHC at rest as defined by the 2015 European Society of Cardiology recommendations for PH.[5] The cardiac index (CI) was calculated by dividing CO by the body surface area. A CI of ≥2.5 L/min/m^2 was accepted as the cutoff value for predicting good clinical status in PH patients.[6]

Overall mortality was defined as the rate of death from all causes within the study population during the mean 5-year (min 1 year–max 13 years) follow-up period. Deaths due to worsening of the disease and sudden cardiac death were included as mortality data. Information regarding mortality was retrieved from hospital records and the national death information online database. In this study, risk assessment of patients at the time of the first catheterization was made using a four-layer risk assessment tool based on the REVEAL 2.0 Risk Score and based on refined cut-off levels for World Health Organization-functional class, 6-min walking distance (6MWD), and serum levels of N-terminal pro-B-type natriuretic peptide (NT-pro-BNP). Patients were also categorized as low, intermediate-low, intermediate-high, or high risk.[7]

For RHC procedures, a standard protocol was followed for all patients with clinical indications. The interventions were performed through the right femoral route. At rest, measurements were made with the Swan-Ganz catheter and blood samples were collected from both the systemic and pulmonary arteries, and CO and CI were determined using the indirect Fick method.

Echocardiography was performed on patients suspected to have PH using two-dimensional and Doppler examinations with the Vivid 5 system and a 3.5 MHz transducer (GE Vingmed Ultrasound AS, Horten, Norway). Risk stratification based on

echocardiographic findings at the time of PH diagnosis, defined as the presence of at least two criteria from the three categories of peak tricuspid regurgitation velocity and other "echo findings suggestive of PH," was estimated using the low, intermediate, and high-risk grouping system defined in the 2015 European Society of Cardiology PH Guidelines.[5] In addition, echocardiography was performed in terms of the risk of developing PH in the outpatient follow-up of the patients. Repeated RHC procedure was performed in patients who developed PH or had an increased risk of PH according to the guidelines in symptoms, 6MWT, echocardiography, and laboratory values from risk assessment parameters in repeated controls. Only patients with mPAP ≥25 mm Hg, PVR ≥3 WU, and PAWP <15 mm Hg, that is, those diagnosed as PAH in the follow-up RHCs were initiated PAH-specific treatment. The descriptive data of these patients who were initiated specific PAH treatment during the follow-up period are presented separately.

Statistical Analysis

Disease and patient characteristics, as well as study parameters, were described using descriptive statistics (mean, standard deviation [SD], number, and frequency). Quantitative data were expressed as mean±SD, while categorical data were presented as n (%). Normality was evaluated using the Kolmogorov–Smirnov test. Pearson correlation analysis was conducted to evaluate the correlation of the parameters with each other. The variance of categorical variables was assessed using Chi-square test. Comparison of parameters between the two groups was carried out using independent samples t-test. All-cause mortality data were obtained from the database and patients were censored at the date of last follow-up. Kaplan–Meier method was used to estimate survival, with censoring at the date of last follow-up. All statistical analysis was conducted using SPSS (v.21) statistical package program (IBM Corp. Armonk, NY, USA).

Results

A total of 395 diagnostic RHC was performed with the suspicion of PH between 2008 and 2021. The study cohort included a total of 140 treatment naive patients (35.4%) who had a measured mPAP values <25 mmHg, during the primary diagnostic RHC between 2008 and 2021. Two patients were excluded due to constrictive pericarditis and one patient because of severe pulmonary stenosis. The mean age at inclusion was 53.1 ± 14.8 years and the mean follow-up period was 4.92 ± 3.13 (min 1–max 13) years. Most of the study population consisted of women (n = 102; 74.5%).

Table 1 depicts the general comparison of the patients with mPAP <21 mmHg with those with an mPAP of 21–24 mmHg. Patients in the mPAP 21–24 mmHg group were older (P = 0.026) and predominantly women (87.5%). Patients with a mPAP of 21–24 mmHg tended to have higher body mass index but the difference was not statistically significant. As expected, prognostic clinical markers including NT-pro-BNP levels and 6MWD were better in the group with mPAP <21 mmHg. However, there were no significant differences between the groups regarding the renal functions, hemoglobin levels, and comorbidities including diabetes, hypertension, coronary artery disease, and atrial fibrillation.

Most of the procedures were performed with a suspicion of pre-capillary PH (n = 98, 71.5%). Among the remaining 54 patients in this group, 20 patients had repaired or unrepaired congenital heart disease (CongHD), two patients before planned liver transplantation, and 20 patients (14.6%) had previous history of pulmonary embolism, and 12 had systemic sclerosis. The other indications were PH due to valvular heart disease (n = 10, three patients with aortic stenosis, three with mitral stenosis, and three mitral regurgitation), and PH due to left heart disease (n = 20, 7%). Nine (6.6%) patients had Group 3 PH, that is, PH due to lung disease related to hypoxia, seven patients had idiopathic pulmonary fibrosis, and two patients had chronic obstructive pulmonary disease. Finally, RHC was applied to 5 (3.6%) patients for evaluation of Group 5 PH.

Table 2 presents the comparison of the echocardiographic and catheterization data of the groups. Approximately 90% of patients who underwent RHC had a TRV >2.8 m/s on transthoracic echocardiography. All echocardiographic parameters related to PH were worser in the group with mPAP of 21–24 mmHg than the others. Echocardiographic signs suggestive intermediate and high risk of PH were detected in the majority of the patients (67.7%) in the 21–24 mmHg group and also in this group, the number of patients with low ejection fraction of the right ventricle ejection fraction (RVEF) was higher (RVEF >50%, 53%, P = 0.006), the right atrium (RA) was significantly dilated (RA area >18 cm^2 (72.7%) and tricuspid circular plane systolic excursion/systolic PAP ratio was lower (TAPSE/sPAP ratio 0.19–0.32, 31.4%, P = 0.010). In the baseline RHC evaluation, PAWP was significantly higher (10.97 + 3.73 vs. 8.22 + 2.76, P = 0.0001) and CI was significantly lower (3.07 ± 0.74, P = 0.001) in the 21–24 mmHg group compared to those with a mPAP of <21 mmHg. Although the CI was lower in the 21–24 mmHg group, CI was >2.5 in 85% of all patients indicating that a high proportion of our study population had good clinical status.

Baseline four-strata risk stratification made during the first RHC (Table 1) revealed that patients with mPAP <21 mmHg were mostly in the low-intermediate group (38.5%), meanwhile the 21–24 mmHg group mostly has high-intermediate risk (46.7%), but the difference between groups did not reach to a statistically significant level.

During the follow-up, a total of 12 patients have undergone repeated RHC and those with mPAP ≥25 mmHg and PVR>3 were initiated PAH-targeted therapy (Table 3). A total of 27.7% of those with mPAP range 21–24 mmHg showed a progression to definite PAH at follow-up. Among these patients, seven had scleroderma, four had pulmonary thrombo-embolism (PTE), and one unrepaired CongHD. Of the patients receiving PAH-specific therapy, only two scleroderma patients were receiving combination therapy. Nine of these 12 patients (75%) were in the mPAP 21–24 mmHg group (three PTE and six scleroderma patients). One of the scleroderma patients had initiated bosentan therapy despite the mPAP of 18 mmHg due to the digital ulcers of scleroderma and other six patients were in the mPAP 21–24 mmHg range group. It was noted that six of the 13 scleroderma patients (46.1%) included in the study died, and only two of these six patients were receiving PAH-specific (pulmonary vasodilator) therapy. There was no difference between the two groups in terms of drug use distribution (P = 0.56).

Table 1. Demographic and Clinical Characteristics by mPAP Categorization

Characteristics	**mPAP <21 mmHg (n = 102)**	**mPAP 21–24 mmHg (n = 35)**	***P***
Age (years) mean±SD	51.5±15.1	57.97±12.8	0.026
Gender n (%)			
Female	72 (70.6)	30 (87.5)	0.077
Male	30 (29.4)	5 (14.3)	
Follow-up duration, years, mean±SD	5.06±3.13	4.57±3.13	0.429
BMI (kg/m²), mean±SD	25.95±4.50	27.84±5.48	0.069
PH group n (%)			
1	61 (59.8)	11 (31.4)	
2	18 (17.6)	13 (37.1)	
3	6 (5.9)	3 (8.6)	
4	12 (11.8)	8 (22.9)	
5	5 (4.9)	0	
Comorbidities n (%)			
Diabetes mellitus	16 (15.7)	7 (20)	0.556
Hypertension	8 (7.8)	4 (11.4)	0.517
Coronary artery disease	7 (6.9)	0	
WHO-FC (%)			
Class 1	17 (16.7)	1 (2.9)	0.07[a]
Class 2	71 (69.6)	22 (62.9)	
Class 3	12 (11.8)	12 (34.3)	
Class 4	2 (2)	0	
Rhythm on ECG (%)			
SR	91 (89.2)	28 (80)	0.134
AF	11 (10.8)	6 (17.1)	
6MWD m; mean±SD	361±100	319±88	0.281
Laboratories			
NT-proBNP ng/L; mean±SD	201±95	379±75	0.37
Hemoglobin, g/dL; mean±SD	12.9±1.2	13±2.3	0.236
GFR, mL/min/1.73 m² (<60) (n, %)	12 (12.4)	3 (9.1)	0.610
Baseline four-strata risk (n, %)			
Low	21 (32.3)	2 (6.7)	0.05[a]
Intermediate-low	25 (38.5)	10 (33.3)	
Intermediate-high	11 (16.9)	14 (46.7)	
High	8 (12.3)	4 (13.3)	
Follow-up[b]			
Addition of PAH-specific treatment (n, %)	3 (2.9)	9 (27.7)	0.56
Survival, (n, %)			
Alive	79 (77.5)	22 (62.9)	0.063
Excitus	23 (22.5)	13 (37.1)	

AF, Atrial fibrillation; BMI, Body mass index; BP, Blood pressure; ECG, Electrocardiography; GFR, Glomerular filtration rate; HR, Heart rate; mPAP, Mean pulmonary artery pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PH, Pulmonary hypertension; SR, Sinus rhythm; WHO-FC, World Health Organization- functional class; 6MWD, 6-min walking distance; [a], Chi-squared test; [b], Except follow-up data all parameters belong to baseline evaluation.

Table 2. Baseline Hemodynamic and Echocardiographic Characteristics by mPAP Categorization

Variables	mPAP <21 mmHg (n = 102)	mPAP 21–24 mmHg (n = 35)	*P*
Echocardiography			
LVEF (>55%), n (%)	90 (83.3)	26 (68.6)	**0.036**[a]
RVEF (>50%), n (%)	83 (80)	19 (53.4)	**0.006**[a]
TAPSE/ sPAP n (%)			
>0.32	71 (84.5)	20 (57.1)	**0.010**[a]
0.19–0.32	10 (11.9)	11 (31.4)	
<0.19	3 (3.6)	0	
RA area >18 cm^2 n (%)	44 (44.2)	24 (72.7)	**0.008**
TRV m/s mean±SD	3.27±0.69	3.18±0.48	0.484
TRV m/s n (%)			
<2.8	4 (4.7)	3 (10.3)	0.545[a]
2.8<...<3.5	58 (68.2)	19 (65.5)	
>3.5	23 (27.1)	7 (24.1)	
Echocardiographic signs suggestive of PH, n (%)	42 (44.2)	21 (67.7)	**0.023**
Right heart catheterization			
RA Pressure, mmHg	7.14 ± 3.65	7.71 ± 4.35	0.48
PAWP, mmHg	8.22 ± 2.76	10.97 ± 3.73	**0.0001**
PVR, Woods units n (%)			
≤ 2	52 (50.9)	19 (54.2)	0.858[a]
> 2	47 (46)	16 (45.7)	
Cardiac output, L/min mean ± SD	5.36 ± 2.04	5.60 ± 1.41	0.483
Cardiac index, L/min/m^2 mean ± SD	3.98 ± 1.15	3.07 ± 0.74	**0.001**
Cardiac index, L/min/m^2 (n, %)			
● ≥ 2.5	85 (87.6)	24 (82.8)	0.501[a]
● < 2.5	12 (12.4)	5 (17.2)	

LVEF, Left ventricular ejection fraction; mPAP, Mean pulmonary artery pressure; PAWP, Pulmonary arterial wedge pressure; PH, Pulmonary hypertension; PVR, Pulmonary vascular resistance; RA, Right atrial; RVEF, Right ventricular ejection fraction; TAPSE/sPAP, Tricuspid annular plane systolic excursion/systolic pulmonary artery pressure; TRV, tricuspid regurgitation velocity; [a], Chi-squared test.

Table 3. List of Patients-initiated PAH Specific Therapy with the Diagnosis of PAH during Follow-up

Patient No	Age (years)	Sex	Baseline RHC; mPAP (mmHg)	Flow-up RHC* timing (years)	PAH etiology/ group	PAH specific treatment	Survival outcome
1.	44	Male	18	2	CHD	Macitentan	Alive
2.	63	Female	19	2	PTE	Macitentan	Alive
3.	71	Female	18	7	SS	Bosentan	Excitus
4.	70	Female	24	2	PTE	Riociguate	Alive
5.	64	Female	24	1	PTE	Bosentan	Alive
6.	68	Female	22	3	PTE	Riociguate	Alive
7.	73	Female	22	5	SS	Iloprost	Alive
8.	69	Female	21	5	SS	Bosentan	Excitus
9.	73	Female	22	4	SS	Iloprost	Excitus
10.	75	Female	23	3	SS	Macitentan	Excitus
11.	53	Female	23	4	SS	Combined Macitentan and Tadalafil	Alive
12.	67	Female	21	3	SS	Combined Bosentan and Tadalafil	Alive

CHD, Congenital Heart disease; mPAP, Mean pulmonary artery pressure; PAH, Pulmonary arterial hypertension; PTE, Pulmonary thromboembolism; RHC, Right heart catheterization; SS, Systemic sclerosis. *Only the time between two RHCs was recorded, as not all data from the follow-up RHCs were available.

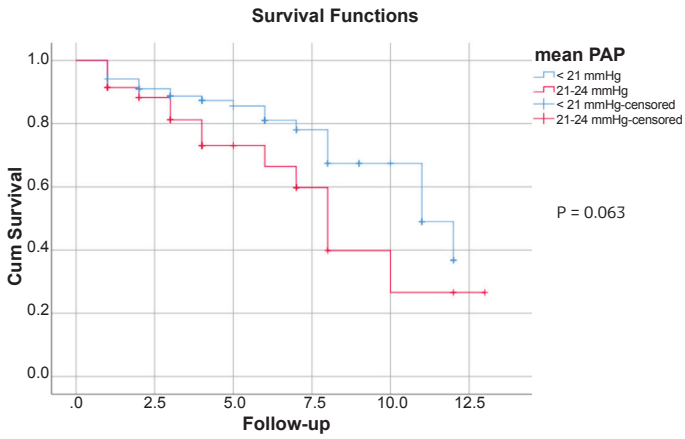

Figure 1. Comparison of survival between groups during follow-up. mPAP <21 mmHg: Mean 9.571 ± 0.45 (95% CI 8.68–10.45). Median 11 ± 1.37 (95% CI 8.30–13.69). mPAP 21–24 mmHg: Mean 7.92 ± 0.92 (95% CI 6.16–9.69). Median 8.00 ± 0.68 (95% CI 6.66–9.33).

During the follow-up, 23 patients (22.5%) in the mPAP <21 mmHg group and 13 (37.1%) in the mPAP 21–24 mmHg group were died (*P* = 0.063) (Figure 1). Survival rates were as follows; 91% of the patients were alive at the end of the 1st year, 88% were alive at the end of the 2nd year 81% at the end of the 3rd year, 73% at the end of the 4th year, and 73% were alive at the end of the 5th year. The three leading causes of death were cardiovascular (n = 20 [14.5%]), respiratory (n = 8 [5.9%]), and systemic sclerosis (n = 6 [4.3%]) in our all-study population. Among the 13 deaths in the mPAP 21–24 mmHg group, four were attributed to systemic sclerosis, four to congestive heart failure, two to malignancies, and three to coronary artery disease. In the mPAP <21 mmHg group, causes of death included early infection after liver transplantation (two cases), chronic kidney failure (one case), congestive heart failure (three cases), heart failure due to CongHD (five cases), chronic obstructive pulmonary disease (two cases), malignancy (one case), idiopathic pulmonary fibrosis (five cases), and systemic sclerosis lung involvement (three cases). All-cause mortality rates were similar in both groups, but scleroderma patients were found to have a mortality rate of approximately 50% in the mPAP 21–24 mmHg group. In the bivariate Pearson-correlation analysis of the variables, there was no significant finding except a negative correlation between mPAP with body mass index.

Discussion

This single-center observational study provided important insights into the long-term prognosis of patients with an mPAP range of 21–24 mmHg. (1) Patients with a mPAP value in the range of 21–24 mmHg tended to have a poorer prognosis in terms of progression to define PH and/or all-cause mortality than those with a mPAP <21 mmHg. (2) Right ventricular involvement was more prominent and echocardiographic signs suggestive of PH were more frequent in individuals with mPAP value in the range of 21–24 mmHg than those with a mPAP <21 mmHg. (3) Poor prognostic signs (high PAWP and low CI) were significantly higher in individuals with mPAP range 21–24 mmHg than those with a mPAP <21 mmHg. (4) Overall, patients with systemic sclerosis tended to have a worser prognosis in both groups.

There is still no complete consensus regarding the upper limits of the normal range of mPAP which is the most important criteria in the diagnosis of PH. In the guidelines, the threshold for diagnosing PH and initiating medication has been revised several times particularly with a lower threshold.[3] This has raised concerns among some researchers that it may increase the over diagnosis of precapillary PH and lead to the initiation of pH-targeted treatment in more patients.[8] On the other hand, earlier treatment may be necessary in certain high-risk groups. Therefore, there is a need for better characterization of the individuals previously referred as "borderline PH" with a mPAP values of 21–24 mmHg. However, there is a scarcity of studies addressing this particular population. An increase in the number of pre-capillary PH patients (12.1%) was reported in a single-center and retrospective study of 58 patients, conducted after the recommendation of the sixth WSPH Symposium revising the hemodynamic definition of PH with a mPAP value of >20 mmHg.[8] However, in our study, it was 9.3%, similar to that was predicted in the 6th WSPH (<10%).[2] Another study which included 32 patients at mPAP 21–24 mmHg group reported that the mPAP 21–24 mmHg group was older, similar to our study group. Differently, cardiac comorbidities and/or impaired lung functions (47% vs. 16%, *P* = 0.001, respectively) were significantly more frequent in the mPAP 21–24 group compared with patients with resting mPAP of <21 mmHg. This result is not surprising since the study was conducted in a pulmonology center and the study population has a mean age of 65.8 ± 2.5 years.[9]

In a nation-wide large multicenter retrospective cohort, Maron et al.[10] examined the survival of patients with borderline elevated mPAP compared with those categorized as mPAP ≤18 mmHg and mPAP ≥25 mmHg. Patients with borderline PH which was defined as 19–24 mmHg compromised the 23.2% of all the study population and more than >90% were male. At 5 years, mortality rates were 23.3% for those mPAP ≤18 mmHg, 29.9% for borderline PH (mPAP 19–24 mmHg), and 48.0% for those with ≥25 mmHg. In the mPAP ≥25 mmHg group, criteria that were significantly associated with mortality were PAWP of >15 mmHg or PVR of ≥3 mmHg. In the subgroup analysis performed after the exclusion of this value group (PAWP of >15 mmHg or PVR of ≥3 mmHg), which is considered as high-risk criterion, the difference in all-cause mortality between the borderline PH and the normal PH groups was similar. As a result, it was concluded that having a borderline PH was independently associated with increased risk of all-cause mortality and hospitalization.[10] In contrast to these studies, we did not include an additional group of patients with mPAP >25 mmHg at baseline, as PAH-specific therapy was initiated in almost all of our patients with mPAP >25 mmHg in accordance with the recommendations of the relevant guidelines. Our analyses are based on the baseline assessment (data) and we only evaluated the study group to determine whether these patients were diagnosed with PAH at follow-up. Interestingly, PAWP values measured at baseline RHC were significantly higher in the 21–24 mmHg group than in the <21 mmHg group. It should also be noted that we reached

this conclusion in patients with mild mitral valve insufficiency and moderate heart failure, and these patients were included in Group 2 in the foreground for differentiation of PHT due to valvular cardiomyopathy. Despite the low CI value in this group, the overall clinical status of the patient population was good, suggesting that most of the patients did not fall into the high-risk category.

In another retrospective but single-center sample (n = 4343), Assad et al.[4] explored the survival in borderline PH (mPAP 19–24 mmHg and half were male) compared with groups mPAP ≤18 mmHg and mPAP ≥25 mmHg. They reported the 5-year survival for those with borderline PH as 75% meanwhile, 83% for those with normal mPAP, and 59% for patients with mPAP ≥25 mmHg. In both studies, all patients who underwent RHC with any indication were enrolled. However, our study covered only those who underwent RHC with a suspicion of PH or unexplained dyspnea. In our cohort, patients with baseline mPAP range 21–24 mmHg had a survival rate of 73% at the end of 5 years, and unadjusted 5-year survival was 70% in our patients who developed PH. Moreover, our population were consisting predominantly female patients (87.5%).

Douschan et al.,[11] in a retrospective and prospective cohort with un-explained dyspnea or at risk for PH, investigated the all-cause mortality in sub-normal, upper-normal, borderline, and manifest PH patients followed for a maximum of 6 years (mean 3.8 years). In their real-life multi-center cohort, survival was associated with clusters of mPAP with thresholds at 17 and 26 mmHg. Even mildly increased mPAP in the range between 17 and 20 mmHg was associated with a decreased physical capacity and survival, although this was largely attributed to advanced age and comorbidities.

Mild or borderline PH associated with increased mortality was also emphasized in two separate meta-analyses.[12,13] The first meta-analysis included 12 studies (eight RHC and seven echocardiograms) with a mean follow-up of 5.2 years (min 1.6–max 8).[12] Compared with the referent group (mPAP <19 mmHg), mild PH (lower limit mPAP of 19 to 21.5 mmHg and an upper limit mPAP of 25 mmHg) was associated with an increased risk of all-cause mortality (risk ratio, 1.52; 95% CI, 1.32–1.74; $P < 0.001$; I^2=47%). The authors particularly emphasized that the association between mildly elevated mPAP and increased mortality remained consistent, regardless of whether mPAP is estimated using echocardiography or measured through RHC. In the other meta-analysis of eight studies with mean/median follow-up duration ranged from 2.1 to 4.2 years (min 1, max 7.5 years), mildly elevated PH group was defined as mPAP of >20 mmHg and <25 mmHg.[13] This meta-analysis showed that patients with mildly elevated mPAP were 1.81– 2.45 times more likely to progress to PH than individuals with normal mPAP and all-cause mortality was significantly higher in the mildly elevated mPAP group than subjects with normal mPAP (hazard ratio, 2.48; 95% CI, 1.69–3.64).

Another important aspect of our study that should be noted is the increased mortality in patients with systemic sclerosis and borderline PAP hemodynamics. PAH developed in 53.8% of our patients with systemic sclerosis during the follow-up, and the mortality rate was 50% in the mPAP 21–24 mmHg group despite treatment. Connective tissue disease (CTD) associated PAH, is known to have poor prognosis and early therapeutic intervention is recommended, but whether borderline PAH cases can be treated without symptoms remains controversial.[3] In the DETECT population, 15% of all patients presented with borderline PAP hemodynamics. Although this percentage may vary in the general scleroderma population, the borderline population is considered to be an important subgroup because of the strict inclusion and exclusion criteria of the DETECT study.[14] In a prospective and observational study with a retrospective component, involving 161 patients from a single center, the frequency of borderline PH before and after the DETECT algorithm was investigated.[15] A follow-up RHC, performed after a mean of 2.4 ± 1.8 years, revealed that 39% of patients with borderline PH had developed PAH. These findings, along with our present study might support the early initiation of PAH-targeted therapy in scleroderma patients with mildly elevated mPAP. However, it should be noted that lung lesions, left heart disease, and/or pulmonary venous lesions may pose obstacles to the use of pulmonary vasodilators in scleroderma-associated PAH cases.[16] The ongoing single-center, prospective, randomized, double-blind, parallel group, placebo-controlled, phase IIA screening, and clinical trial (NCT0229061 access date: 2020) will provide insights to the efficacy of early treatment in scleroderma patients with borderline PH before progression to PAH.[17] Likewise, publications from various PH centers with new PH definition have begun to emerge. For example, in a study conducted by Tanyeri et al.[18] from Türkiye using this new definition criteria, TRV and additional echocardiographic parameters suggestive for PH were significant in those with mPAP ≥25 mmHg, meanwhile only TRV was significant in the 21–24 mmHg Group.[18] It is obvious that as the number of studies based on the new PH definition increase, we will be able to understand the physiology and prognosis of those with an mPAP in the range of 21–24 mmHg.

Strengths and Limitations

The retrospective nature of our study can be acknowledged as a significant limitation. In addition, the fact that the data were collected from a single center with limited number of patients is another limitation. However, it is important to highlight that our study represents the longest follow-up conducted in a population with an mPAP of 21–24 mmHg spanning a period up to 13 years. This extended duration of observation of the natural history is the main strength of our study.

The fact that our center predominantly receives referrals for CongHD as a specialized PH center may indeed impact the generalizability of our findings in the mPAP of 21–24 mmHg population. In CongHD-related PH, patients with low risk at the initial evaluation have a better clinical course. Early and combination treatments are controversial, as the risk of mortality increases in patients with initial and high risk. A recent study has indicated that abbreviated and simplified risk assessment methods can be employed for CongHD associated PAH.[19] The study suggests that patients who cannot achieve low risk at follow-up may benefit from more aggressive use of existing therapies, while patients classified as low risk at baseline have a favorable prognosis. We could not detect a statistically significant difference in risk classification possible due to the

higher frequency of CongHD in our study compared to the other centers in similar studies.[20] And finally, although patients with systemic sclerosis in the mPAP 21–24 mmHg group were mostly received PH diagnosis and initiated PAH-specific treatment and the mortality rate was found to be 50%, we could not perform subgroup analysis due to the small sample size.

Conclusion

The present single-center real-life data provided important insights to the natural course of patients with a mPAP range of 21–24 mmHg. Individuals with borderline mPAP values (21–24 mmHg) may still experience an increased risk of all-cause mortality and progression to overt PAH even in the absence of comorbidities. Patients with a mPAP value in the range of 21–24 mmHg tend to have a poorer prognosis than those with a mPAP <21 mmHg. Right ventricular involvement is a more prominent echocardiographic sign of suggestive of PH, and is more frequent in individuals with mPAP value in the range of 21–24 mmHg than those with a mPAP <21 mmHg. Patents with mPAP range 21–24 mmHg with systemic sclerosis seem to be a distinct group at high risk that may deserve early treatment. Larger multicenter clinical trials with long-term follow-up are warranted to clarify the effect of early treatment options in these high-risk patients.

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References

1. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J*. 2009;34(4):888-94. [CrossRef]
2. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J.* 2019;53(1):1801913. [CrossRef]
3. Humbert M, Kovacs G, Hoeper MM, et al.; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;43(38):3618–731. Erratum in: *Eur Heart J.* 2023;44(15):1312. [CrossRef]
4. Assad TR, Maron BA, Robbins IM, et al. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol.* 2017;2(12):1361-8. [CrossRef]
5. Galiè N, Humbert M, Vachiery JL, et al.; ESC Scientific Document Group. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016;37(1):67–119. [CrossRef]
6. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J.* 2012;39(3):589–96. [CrossRef]
7. Hoeper MM, Pausch C, Olsson KM, et al.. COMPERA 2.0: A refined four-stratum risk assessment model for pulmonary arterial hypertension. *Eur Respir J.* 2022;60(1):2102311. [CrossRef]
8. Sinan ÜY, Çetinarslan Ö, Arat Özkan A, Ersanlı MK, Küçükoğlu MS. The impact of the new world symposium on pulmonary hypertension definition of pulmonary hypertension on the prevalence of pre-capillary pulmonary hypertension. *Turk Kardiyol Dern Ars.* 2019;47(7):594–8.
9. Kovacs G, Avian A, Tscherner M, et al. Characterization of patients with borderline pulmonary arterial pressure. *Chest.* 2014;146(6):1486–93. [CrossRef]
10. Maron BA, Hess E, Maddox TM, et al. association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: Insights from the veterans affairs clinical assessment, reporting, and tracking program. *Circulation.* 2016;133(13):1240–8. [CrossRef]
11. Douschan P, Kovacs G, Avian A, et al. Mild elevation of pulmonary arterial pressure as a predictor of mortality. *Am J Respir Crit Care Med.* 2018;197(4):509–16. [CrossRef]
12. Kolte D, Lakshmanan S, Jankowich MD, Brittain EL, Maron BA, Choudhary G. Mild pulmonary hypertension ıs associated with ıncreased mortality: A systematic review and meta-analysis. *J Am Heart Assoc.* 2018;7(18):e009729. [CrossRef]
13. Xue L, Yang Y, Sun B, Liu B, Zeng Q, Xiong C. Mildly elevated pulmonary arterial pressure ıs associated with a high risk of progression to pulmonary hypertension and ıncreased mortality: A systematic review and meta-analysis. *J Am Heart Assoc.* 2021;10(7):e018374. [CrossRef]
14. Kovacs G, Olschewski H. Borderline pulmonary pressures in scleroderma - a 'pre-pulmonary arterial hypertension' condition? *Arthritis Res Ther.* 2015;17(1):123. [CrossRef]
15. Hoffmann-Vold AM, Fretheim H, Midtvedt Ø, et al. Frequencies of borderline pulmonary hypertension before and after the DETECT algorithm: Results from a prospective systemic sclerosis cohort. *Rheumatology (Oxford).* 2018;57(3):480–7. [CrossRef]
16. Yoshifuji H, Kinoshita H. Management of borderline pulmonary arterial hypertension associated with connective tissue diseases. *Nihon Rinsho Meneki Gakkai Kaishi.* 2014;37(6):454–61. Japanese. [CrossRef]
17. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J*. 2019;53(1):1801914. [CrossRef]
18. Tanyeri S, Tokgöz HC, Karagöz A, et al. Reappraisal of the transthoracic echocardiographic algorithm in predicting pulmonary hypertension redefined by updated pulmonary artery mean pressure threshold. *Anatol J Cardiol.* 2023;27(6):348–59. [CrossRef]
19. Pan Z, Marra AM, Benjamin N, et al. Early treatment with ambrisentan of mildly elevated mean pulmonary arterial pressure associated with systemic sclerosis: A randomized, controlled, double-blind, parallel group study (EDITA study). *Arthritis Res Ther.* 2019;21(1):217. [CrossRef]
20. Yaylalı YT, Yağmur B, Sinan ÜY, et al. Risk assessment tool implementation in congenital heart disease-associated pulmonary arterial hypertension. *Anatol J Cardiol.* 2023;27(8):479–85. [CrossRef]