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Clinical and hemodynamic profiles of elderly patients with pulmonary arterial hypertension: a single center, prospective study

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Abstract

Backgrounds Pulmonary arterial hypertension (PAH) was previously considered an illness that affects mostly the young, but now it is also increasingly recognized in the elderly. The aim of this study was to compare the features of elderly versus younger patients diagnosed with PAH, and to define the prognostic factors which affect their long-term survival. **Methods** In this prospective, single center study, the clinical, echocardiographic, hemodynamic characteristics, and the outcomes of younger (18–65 years) and elderly (≥ 65 years) patients with definitive diagnosis of precapillary PAH were compared. **Results** A total of 119 patients were analyzed in this study; 43 were elderly (mean age: 71.5 ± 5.5 years), while 76 were non-elderly (mean age 44.5 ± 15.2 years). During the mean follow-up duration of 26.8 ± 25.0 months, 43 deaths occurred, 17 of which were among the elderly group, with 28 among non-elderly group. Comparison of baseline parameters showed that 6 min walking distance, hemoglobin levels, pulmonary artery pressures and pulmonary vascular resistance were significantly lower; and estimated glomerular filtration rate, body mass index, E/e' and pulmonary capillary wedge pressure were significantly higher in the elderly group than in the younger group. Survival analysis demonstrated that the independent predictors of death were tricuspid plane annular systolic excursion (TAPSE; HR: 1.272, 95% CI: 1.079–1.499, $P = 0.004$) and uric acid (HR: 1.291, 95% CI: 1.042–1.600, $P = 0.019$) in the elderly group. In contrast, in the non-elderly group, higher brain natriuretic peptide (HR: 1.002, 95% CI: 1.001–1.004, $P < 0.001$) and higher right atrial pressure (HR: 1.128, 95% CI: 1.026–1.241, $P = 0.013$) values were the only parameters associated with mortality. **Conclusions** Our data suggest that elderly PAH patients have a unique clinical and hemodynamic profile, with totally different prognostic markers compared to younger PAH patients.

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1 Introduction

The term pulmonary arterial hypertension (PAH) describes a group of diseases characterized by pre-capillary pulmonary hypertension in the absence of known causes such as lung disease, or left heart diseases.[1] It is characterized by a progressive increase in pulmonary vascular resistance (PVR), leading to right heart failure and, ultimately, death.[2] PAH was previously considered to be an illness that affects mostly the young; nowadays, it is also increasingly recognized in the elderly.[3–6] With the emergence of effective therapies, the awareness of PAH has risen among both patients and physicians. At the same time, the population of most western countries is aging. Recent data from Europe and the US suggest that the demographics of patients diagnosed with PAH are changing.[7–9] Nowadays, it is not uncommon to see patients being diagnosed with PAH in their seventies or eighties.[8] In the National Institutes of Health (NIH) registry of primary pulmonary hypertension, which was one of the first registries concerned with PAH, the mean age at diagnosis was 36 years. This registry assembled data between 1981 and 1985 when no targeted drug therapies for PAH were available.[10,11] In the more recent US-based Registry for the evaluation of early and long-term

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pulmonary arterial disease management (REVEAL), the mean age at diagnosis was 50 years, with 5% of these patients were diagnosed at ≥ 75 years of age.[3] Comparable data were reported from the French National PAH registry, where the average age at diagnosis of PAH was 52 years.[6] Elevated estimated systolic pulmonary artery pressure (sPAP) by echocardiography and increased left ventricular (LV) diastolic pressures are common in elderly patients, and pulmonary hypertension (PH) associated with heart failure with preserved ejection fraction (HFpEF) is the most common cause of PH in older adults.[12,13] Understanding the causes and characteristics of PH in elderly patients, particularly distinguishing between HFpEF and PAH, is especially important for the appropriate choice PH therapies in this population. In addition, it is uncertain whether their survival is influenced primarily by PAH progression, and right ventricular (RV) dysfunction, or by their co-morbidities.[5] The objectives of the present study were to compare the features of elderly versus younger patients diagnosed with PAH, and to define the prognostic factors which affect their long-term survival.

2 Methods

2.1 Patients

Consecutive adult patients with definitive PAH who attended the PAH Clinic at the Department of Cardiology, School of Medicine, Dokuz Eylul University (Izmir, Turkey) between January 2008 and December 2015 were prospectively screened for inclusion in this prospective study. All patients met the diagnostic criteria for the definitive diagnosis of pre-capillary PAH (mean PAP ≥ 25 mmHg and pulmonary capillary wedge pressure ≤ 15 mmHg).[1] Patients with WHO class 1, 4 and 5 PAH were included, whereas those with WHO classes 2 and 3 (non-PAH) were excluded. The Dokuz Eylul University Ethics Committee approved the study protocol (No. 2138-GOA). Verbal informed consent was obtained from all of the study participants. For the purpose of the current study, patients were divided into elderly (≥ 65 years) and non-elderly (< 65 years) groups. Patients underwent standard evaluation for PH (according to published guidelines) to determine the presence, severity, and cause of PH. Right and left sided heart catheterization, in addition to other standard testing (pulmonary function testing, chest imaging, ventilation-perfusion scanning, and echocardiography), was used to definitively determine the cause of PH in accordance with consensus guidelines. Cardiac catheterization was performed at rest, without sedation, by an experienced cardiologist. During cardiac catheterization systolic, mean and diastolic pulmonary artery pressures ($sPAP_{RHC}$, $mPAP_{RHC}$, $dPAP_{RHC}$), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), cardiac index (CI), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR) were all measured and calculated according to the recommended guidelines.[1]

The following parameters were measured during transthoracic echocardiography: systolic PAP ($sPAP_{DE}$); RV end-diastolic diameter; right atrial area (RAA); tricuspid plane annular systolic excursion (TAPSE); RV tissue Doppler systolic velocity (RVS), and; RV Tei index.[14] Baseline evaluation of the patients also included the following: New York Heart Association functional class (NYHA FC) assessment; routine laboratory tests; brain natriuretic peptide (BNP); and 6-minute walking distance (6MWD). Patients were followed-up periodically at 3-month intervals. Follow-up visits included a physical examination, NYHA FC assessment, BNP testing, 6MWD, routine laboratory testing and comprehensive echocardiography. The survival period was calculated either as the number of months from initial diagnosis up to December 2015, which was the end of the follow-up period in this study, or up to patient death if that occurred first.

2.2 Statistical analyses

All statistical analyses were performed using the SPSS-statistical package, version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows. To test the distribution pattern, the Kolmogorov-Smirnov method was used. Data are summarized as the mean ± SD, median (interquartile range), or *n* (%). Analysis of variance was used to compare data between the tertiles displaying normal distribution. Either the independent Student's *t* test or Mann–Whitney *U* test were used to compare continuous variables. Chi square test and/or Fisher's exact test were used to compare categorical variables. The primary endpoint was all-cause mortality. For survival analysis, all patients with more than 6 months of follow-up were censored. To identify the risk factors of death, all variables with $P < 0.05$ in univariate analysis were selected for multivariate Cox regression analysis in both groups. Pearson correlation analysis was used to evaluate the correlation between various parameters.

3 Results

A total of 119 patients (mean: 54.4 ± 18.5 years; range: 18–88 years) with a definitive diagnosis of PAH were included in the study. The mean follow-up duration of the study population was 26.8 ± 25.0 months. According to age group, 43 patients were elderly (≥ 65 years). The mean age was 71.5 ± 5.5 years, the mean follow-up duration was 21.5

± 19.4 months, and the female ratio was 83.7% in the elderly group. The number of deaths was 17 (39.5%) and the number of hospitalizations for clinical worsening was 13 (30.2%) in this group. The non-elderly group (age < 65 years) consisted of 76 patients. In this group of patients, the mean age was 44.5 ± 15.2 years, the mean follow-up duration was 30.0 ± 27.3 months, and the female ratio was 73.6%. The number of deaths was 28 (36.8%) and the number of hospitalizations for clinical worsening was 22 (28.9%) in this group. Table 1 shows the baseline characteristics of patients in both groups. Elderly group had significantly higher body mass index (BMI) values compared to non-elderly group (27.6 ± 8.3 *vs*. 24.1 ± 6.9 kg/m^2; P = 0.01). In respect to PAH subtypes, although elderly patients had a lower frequency of congenital heart disease compared to non-elderly patients (20.9% *vs*. 34.2%), there was no significant difference between the groups in general (P = 0.582). Elderly patients had a higher frequency of systemic

Table 1. Comparison of baseline clinical parameters between elderly and non-elderly patients with PAH.

	Elderly group (≥ 65 yrs), *n* = 43	Non-elderly group (< 65 yrs), *n* = 76	*P* value
Age, yrs	71.5 ± 5.5	44.6 ± 15.2	**< 0.001**
Female ratio	36 (83.7%)	56 (73.7%)	0.209
BMI, kg/m^2	27.6 ± 8.3	24.1 ± 6.9	**0.01**
HT	33 (76.7%)	26 (34.2%)	**< 0.001**
DM	14 (32.6%)	19 (25.0%)	0.376
Follow-up duration, months	21.1 ± 19.4	300 ± 27.3	0.064
Number of deaths	17 (39.5%)	28 (36.8%)	0.771
Hospitalization for clinical worsening	13 (30.2%)	22 (28.9%)	0.882
PAH etiology			
IPAH	34.9%	29.0%	
Congenital heart disease	20.9%	34.2%	0.582
Connective tissue disease	16.3%	13.3%	
CTEPH	23.3%	17.1%	
Group 5 PAH	4.7%	6.6%	
NYHA FC	3.0 ± 0.6	2.8 ± 0.7	0.160
*BNP, pg/mL	208.0 (337.0)	241.5 (652.5)	0.337
*6MWD, m	300 (198)	370 (203)	**0.002**
$sPAP_{RHC}$, mmHg	67.6 ± 13.3	88.5 ± 25.6	**< 0.001**
$mPAP_{RHC}$, mmHg	39.1 ± 7.3	54.0 ± 16.5	**< 0.001**
*PVR, Wood unit	5.0 (4.3)	8.4 (6.2)	**0.003**
RAP, mmHg	9.2 ± 4.4	10.5 ± 6.6	0.288
CI, L/min per m^2	2.8 ± 1.0	3.0 ± 1.2	0.379
PCWP, mmHg	12.8 ± 5.1	8.1 ± 4.3	**< 0.001**
$sPAP_{DE}$, mmHg	79.3 ± 19.1	88.4 ± 21.8	**0.025**
TAPSE, mm	16.9 ± 5.2	17.4 ± 5.5	0.629
RVS, cm/s	13.1 ± 3.6	12.6 ± 3.6	0.479
RV Tei	0.70 ± 0.43	0.75 ± 0.1	0.842
RAA, mm^2	27.1 ± 9.8	27.0 ± 9.1	0.958
E/e'	12.4 ± 3.9	8.1 ± 2.8	**0.03**
Haemoglobin, g/dL	12.1 ± 2.5	13.5 ± 2.5	**0.010**
Uric acid, mg/dL	7.0 ± 2.5	6.9 ± 2.5	0.904
eGFR, mL/min per 1.73 m^2	66 ± 13.4	83 ± 17.2	**0.006**

Data are presented as mean ± SD, *n* (%) or median (interquartile range). *Mann Whitney *U* test was applied to compare median values between the groups; percentage values were compared between the groups using chi-square test; and Student's *t* test was used to compare mean ± SD between the groups. BMI: body mass index; BNP: brain natriuretic peptide; CI: cardiac index; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HT: systemic hypertension; mPAPRHC: mean pulmonary artery pressure measured on right-heart catheterization; NYHA FC: New York Heart Association functional class; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; 6MWD: 6-min walking distance; $sPAP_{DE}$: systolic pulmonary artery pressure measured by Doppler echocardiography; $sPAP_{RHC}$: systolic pulmonary artery pressure measured on right-heart catheterization; RAP: right atrial pressure; RVS: tissue Doppler right ventricular systolic velocity; RAA: right atrial area; TAPSE: tricuspid plane annular systolic excursion.

hypertension (76.7% *vs*. 34.2%, $P < 0.001$). In terms of clinical and biochemical parameters, 6MWD and hemoglobin levels were significantly lower in the elderly patients (300 *vs.* 370 pg/mL, $P = 0.002$ and 12.1 ± 2.5 *vs*. 13.5 ± 2.5 g/dL, $P = 0.010$ respectively). Estimated glomerular filtration rate (eGFR) were significantly higher in the elderly group (66 ± 13.4 *vs.* 83 ± 17.2 mL/min per 1.73 m^2, $P = 0.006$). Among echocardiographic parameters, $sPAP_{DE}$ was significantly lower in this group (79.3 ± 19.1 *vs.* 88.4 ± 21.8 mmHg, $P = 0.025$). All of the other echocardiographic parameters of RV functions were similar between these two groups. Elderly group had a significantly higher mean E/e' value compared to non-elderly group (12.4 ± 3.9 *vs.* 8.1 ± 2.8 mmHg, $P = 0.03$). Among the catheterization parameters, $sPAP_{RHC}$ (67.6 ± 13.3 *vs.* 88.5 ± 25.6 mmHg, $P < 0.001$), $mPAP_{RHC}$ (39.1 ± 7.3 *vs.* 54.0 ± 16.5 mmHg, $P < 0.001$) and PVR (5.0 *vs.* 8.4 Wood unit, $P = 0.003$) were all significantly lower in elderly patients, whereas cardiac index, and RAP values were similar. Pulmonary capillary wedge pressure was significantly higher in the elderly group (12.8 ± 5.1 *vs.* 8.1 ± 4.3 mmHg, $P < 0.001$).

Among the elderly patients, the risk factors for mortality through univariate analysis were identified as higher sPAP, lower TAPSE and higher uric acid values. In multivariate Cox regression analysis, only the TAPSE (HR: 1.272, 95 % CI: 1.079–1.499, $P = 0.004$) and uric acid (HR: 1.291, 95% CI: 1.042–1.600, $P = 0.019$) emerged as independent predictors of mortality in elderly PAH patients (Table 2).

Among the non-elderly PAH patients, higher BNP, lower 6MWD, higher RAP, lower hemoglobin and the presence of pericardial effusion were significantly associated with death in univariate analysis. However, in multivariate Cox regression analysis, higher BNP (HR: 1.002, 95% CI: 1.001–1.004, $P < 0.001$) and higher RAP (HR: 1.128, 95% CI: 1.026–1.241, $P = 0.013$) values were the only parameters associated with mortality in this group (Table 3).

The correlation analysis of certain clinical parameters with hemodynamic parameters showed that WHO FC, 6MWD and BNP did not correlate with hemodynamic variables (sPAP, PVR, CI, RAP, PCWP) in elderly patients (Table 4). Conversely, PVR was positively correlated with FC ($r = 0.378$, $P = 0.002$) and BNP ($r = 0.365$, $P = 0.003$) in non-elderly patients, but negatively correlated with 6MWD ($r = –0.259$, $P = 0.05$). Again, in this younger group, RAP was positively correlated with FC ($r = 0.397$, $P = 0.001$), but negatively correlated with 6MWD ($r = –0.444$, $P = 0.001$) (Table 5). The correlation between uric acid levels

Table 2. Multivariate Cox regression analysis of parameters associated with death in elderly PAH patients.

	HR	95% CI	*P* value
$SPAP_{RHC}$	0.996	0.961–1.033	0.845
Uric acid	1.291	1.042–1.600	0.019
TAPSE	1.272	1.079–1.499	0.004

PAH: pulmonary arterial hypertension; $sPAP_{RHC}$: systolic pulmonary artery pressure measured on right-heart catheterization; TAPSE: tricuspid plane annular systolic excursion.

Table 3. Multivariate Cox regression analysis of parameters associated with death in non-elderly PAH patients.

	HR	95% CI	*P* value
BNP	1.002	1.001–1.004	< 0.001
6MWD	1.002	0.993–1.003	0.375
RAP	1.128	1.026–1.241	0.013
Haemoglobin	1.158	0.611–1.218	0.401
Pericardial effusion	1.292	0.422–3.956	0.654

BNP: brain natriuretic peptide; 6MWD: 6-min walking distance; RAP: right atrial pressure.

Table 4. Correlation analysis of hemodynamic and clinical variables in elderly patients.

		NYHA FC	6MWD	BNP
$sPAP_{RHC}$	*r*	0.138	–0.115	0.008
	P	0.389	0.551	0.962
PVR	*r*	–0.162	0.061	–0.057
	P	0.325	0.764	0.722
CI	*r*	–0.159	0.226	0.240
	P	0.353	0.289	0.131
RAP	*r*	0.098	–0.220	0.246
	P	0.564	0.280	0.131

BNP: brain natriuretic peptide; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; NYHA FC: New York Heart Association functional class; 6MWD: 6-min walking distance; $sPAP_{RHC}$: systolic pulmonary artery pressure measured on right-heart catheterization.

Table 5. Correlation analysis of hemodynamic and clinical variables in non-elderly patients.

		NYHA FC	6MWD	BNP
$sPAP_{RHC}$	*r*	0.139	–0.119	0.196
	P	0.239	0.348	0.103
PVR	*r*	0.378	–0.259	0.365
	P	0.002	0.05	0.003
CI	*r*	0.010	0.214	–0.248
	P	0.937	0.111	0.048
RAP	*r*	0.397	–0.444	0.206
	P	0.001	0.001	0.109

BNP: brain natriuretic peptide; CI: cardiac index; NYHA FC: New York Heart Association functional class; PVR: pulmonary vascular resistance; RAP: right atrial pressure; 6MWD: 6-min walking distance; $sPAP_{RHC}$: systolic pulmonary artery pressure measured on right-heart catheterization.

and hemodynamic parameters was also analyzed in whole group. Pulmonary artery pressure and PVR did not correlate with uric acid, but RAP had a significant positive correlation (r = 0.233, P = 0.022), while CI had a significant negative correlation (r = –0.276, P = 0.006) with serum uric acid levels in whole study population.

4 Discussion

The key findings of our study include: (1) there is an increasing number of elderly patients in PAH population; (2) there are differences in the clinical invasive hemodynamic profile between elderly and younger patients; (3) there are also differences in prognostic models between elderly and younger patients; (4) there is a relative weakness of previously defined prognostic factors in predicting survival in elderly patients with PAH, and (5) there is a lack of correlation between important hemodynamic and clinical parameters in elderly PAH patients.

In our PAH population, 36.1% of patients were older than 65 years. This was a relatively higher ratio compared to previous registries. In previous PAH registries, the ratio of elderly patients ranged from 13.5%–24%.[15,5] Indeed, a prominently higher ratio of patients with PAH were older than 65 was only observed in COMPERA registry, which was 63%.[6] In this registry one possible explanation for this higher ratio may be the misclassification of patients as IPAH, when they in fact had other causes, such as left heart disease and lung disease. Although all patients fulfilled the hemodynamic criteria for pre-capillary pulmonary hypertension in that registry, some potential pitfalls of this hemodynamic classification in an elderly population cannot be ignored.[6] The main issue of PAH diagnosis in the elderly is to discriminate pulmonary vascular disease from the expected consequences of aging, and from the frequent causes of PH secondary to left heart failure or lung disease. Significant loss of the total capillary lung volume,[16] age-related vascular stiffening which may also affect the pulmonary vascular bed,[17] and a decrease in left heart compliance leading to progressive LV diastolic dysfunction,[18] are all factors that cause an increased PAP in older-aged patients. Therefore, it is not surprising that sPAP shows a significant age-related increase of approximately 1 mmHg per decade.[19] These age-related physiological changes of the cardiovascular and respiratory systems should be kept in mind when evaluating PH in the elderly. In fact, normal aging could either lead to an overdiagnosis of PH, or an underestimation of PAH in this population. Resting wedge pressure can be normal despite subtle LV diastolic dysfunction, which increases with age.[20] Consequently, higher rates of misclassification of PH associated with diastolic heart failure as PAH is more likely in the elderly group. Exercise and saline challenge have been proposed for the identification of occult left-heart disease, however these tools have not yet been validated.[21,22] Interestingly, a cross-sectional study suggested that PAH and HFpEF-PH could be more accurately differentiated through the use of predictive modeling.[23] Old age, the presence of hypertension and coronary heart disease, the absence of right atrial enlargement, higher aortic systolic pressure, higher mean right atrial pressure, and higher cardiac output serve to best differentiate PAH from HFpEF-PH.[23] Although the ratio of the elderly population in our group was not as high as in COMPERA registry, the same drawbacks as listed above may all contribute to this relatively higher ratio.

The second major finding of our study was the marked difference in the clinical and invasive hemodynamic profiles of the elderly and non-elderly patients. Elderly patients had higher BMI values compared to younger patients, and they were more commonly hypertensive. They also had lower eGFR values compared to younger patients, all of which reflect a complex co-morbidity state in elderly PH patients. Among the catheterization parameters, $sPAP_{RHC}$, $mPAP_{RHC}$ and PVR were all significantly lower in the elderly patients, whereas the CI and RAP values were similar and the PCWP was significantly higher compared to younger group. This finding is consistent with previous studies that have demonstrated lower PAP and PVR, but similar CI values in elderly patients compared to young patients.[6,20] Our data confirmed the previous data, as they showed that elderly patients did not present with a more advanced disease, but rather they presented with a milder disease compared with non-elderly patients, as evidenced by the hemodynamic parameters.[6,20] Nevertheless, the similar CI values and echocardiographic RV function parameters (despite the lower PAP and PVR values in our elderly patients) suggest a worse RV adaptation compared to younger patients. This was also observed in the previously defined data suggesting that younger patients tend to have stronger right ventricles capable of preserving cardiac output at a higher PVR than older patients.[6] The higher PCWP together with the higher E/e' values in the elderly group suggest an occult diastolic heart failure in these patients. Although the present PAH guidelines define the precapillary pulmonary hypertension as mPAP $\geq$ 25 mmHg and PCWP $\leq$ 15 mmHg, there is some discussion about the threshold PCWP value. Because normal PCWP values have been found to range from 5 to 12 mmHg in healthy volunteers and classification of patients with PCWP between 12 and 15 mmHg is contraversial.[24] Authors suggest that suspicion for PH-HFpEF should be

raised at values between 12 and 15 mmHg particularly in diuresed patients and/or risk factors for left heart disease (such as systemic hypertension). In our elderly group, 28 patients had PCWP values ranging between 12 and 15 mmHg. For those patients, exercise and fluid challenge tests may be used in discriminating PH-HFpEF and precapillary PH.[21,22,25] However, current guidelines do not recommend these challenge tests in clinical practice due to lack of meticulous evaluation and standardization. In accordance with the current guidelines we did not perform these challenge tests in our patients with PCWP between 12 and 15 mmHg. This may raise the possibility of misclassifying some patients with HFpEF as PAH leading to higher PCWP values observed in our elderly group.

When we looked at the exercise capacity of the patients, FC was similar, whereas 6MWD was significantly lower in the elderly patients compared to non-elderly patients. Poorer exercise capacity despite lower PAP and PVR values suggest that diminished adaptive capacity of RV, age itself and other comorbid diseases may all contribute significantly to poor exercise capacity in elderly patients. We also demonstrated this discrepancy between hemodynamic profile and clinical profile of the elderly PAH patients via correlation analyses. We showed that WHO FC, 6MWD and BNP did not correlate with hemodynamic variables (sPAP, PVR, CI, RAP) in elderly patients. In contrast, in non-elderly patients PVR and CI were all significantly correlated with FC, BNP and 6MWD.

When the prognostic factors in two groups were analyzed separately, we found that in the non-elderly group the classical prognostic factors worked well. Higher BNP, lower 6MWD, higher RAP, lower hemoglobin and the presence of pericardial effusion were all significantly associated with death in univariate analysis. Additionally, in multivariate Cox regression analysis, higher BNP and higher RAP values were the only parameters associated with mortality. As documented in the latest PAH guidelines, BNP, RAP, pericardial effusion and 6MWD were all among the classical prognostic factors in PAH patients.[1] Thus, we can easily conclude that the classical prognostic factors are useful for predicting survival in non-elderly PAH patients. When we looked at the elderly group, the risk factors for mortality through univariate analysis were identified as higher sPAP, lower TAPSE and higher uric acid values. In multivariate Cox regression analysis, only the TAPSE and uric acid emerged as independent predictors of mortality in elderly PAH patients. We thought that the discrepancy between the hemodynamic and clinical profile of the elderly PAH patients due to age itself and other comorbid diseases limited the use of these clinical parameters in predicting survival. This was, therefore, why 6MWD, FC and BNP were not associated with death in elderly patients. However, rather than these parameters, TAPSE, which is a marker of RV systolic function, was useful in predicting mortality. The survival of PAH patients largely depends on the adaptation of the RV to high pulmonary pressures.[2] Although this adaptation is worse in elderly patients, its prognostic value is higher in predicting mortality. This may be due to the relative failure of other hemodynamic and clinical parameters in predicting mortality, or due to the determinative effect of RV functions in prognosis.

The other independent prognostic factor in our elderly patients was serum uric acid level. Previous studies have demonstrated that serum uric acid is elevated in several hypoxic states, such as chronic heart failure,[26] cyanotic congenital heart disease,[27] and obstructive pulmonary disease.[28] It has also been suggested that serum uric acid is an independent predictor of death in patients with chronic heart failure.[29] Two small studies investigated the importance of uric acid level in PAH patients. In a group of 86 PAH patients, Zhag, *et al*.[30] demonstrated that serum uric acid levels were associated with IPAH severity and the severity of ventricular dysfunction. In another study, Li, *et al*.[31] showed that higher serum level of uric acid predicts worse conditions and prognosis in PAH patients. Lung tissue ischemia and reduced renal perfusion secondary to diminished cardiac output may be the main reasons for hyperuricemia in PAH state.[32,33] In our population, we had already demonstrated the association between uric acid levels and cardiac output. Uric acid levels were negatively correlated with CI and positively correlated with RAP in our study. Consequently, serum uric acid levels seem to present the severity of right heart failure in PAH patients. It is also known that increasing age, higher blood pressure, higher cholesterol and higher creatinine levels are all associated with increased serum uric acid levels in the general population.[34–36] However, an age dependent association between uric acid and cardiovascular disease severity had not been described in the previous literature. We think that the close association of serum uric levels with several comorbidities may enable uric acid levels to serve as an overall risk predictor, especially in elderly patients with several comorbid diseases.

4.1 Limitations

Our study has several limitations. Firstly, it is a single-center study and, due to the specialized setting of a PAH Clinic, referral bias may have occurred. The second limitation is the potential risk of misclassification of post-capillary venous hypertension as PAH especially in elderly patients. Although all of our patients fulfilled the hemodynamic cri-

teria for pre-capillary PH we did not perform volume or exercise challenge during right heart catheterization, so that we might have missed some patients with LV diastolic dysfunction. Such tests, however, have not been standardized and are currently not recommended as part of the diagnostic work-up of patients with unexplained PH.[21,22] Finally, despite adjusting for multiple risk factors, it is possible that there might have been residual confounding conditions and medications which may affect the prognosis.

4.2 Conclusions

In conclusion, despite the increasing number of elderly patients who suffer from PAH, their unique profile has not been sufficiently clarified. Our findings suggest that this population has specific clinical and hemodynamic measures. Discrimination of pre-capillary PH and PH-HFpEF is a challenging point particularly in elderly patients with borderline PCWP values and further well validated tests should be defined for this purpose. Comorbid diseases and aging itself may cause an altered hemodynamic profile in these patients, which may sometimes be discrepant with the pulmonary vascular disease itself. However, our findings suggest that RV functions may determine the overall prognosis in such complicated cases with several comorbidities. Also, serum uric acid levels seem to be an important prognostic factor in these patients. In the light of our study and the previous literature data, we think that diagnostic work-up, definitions, treatment goals and the current therapeutic recommendations for patients with PAH may need to be adjusted for elderly patients. Further studies are needed for this purpose.

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