Pulmonary Hypertension Is Associated with Mortality and Cardiovascular Events in Chronic Kidney Disease Patients

Javier Reque^a Ana Garcia-Prieto^a Tania Linares^a Almudena Vega^a
Soraya Abad^a Nayara Panizo^a Borja Quiroga^a Eladio J. Collado Boira^b
Juan Manuel López-Gómez^a

^aDepartment of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, and ^bFaculty of Health Sciences, University Jaime I, Castellon, Spain

Key Words

Pulmonary hypertension · Haemodialysis · Fluid overload · Cardiovascular risk · Outcomes

Abstract

Background: We evaluated the prevalence, determinants and prognosis value of pulmonary hypertension (PH) in non-dialysis chronic kidney disease (CKD) patients. **Methods:** This is a prospective study with stages 3–5 non-dialysis-dependent CKD patients. PH was estimated by Doppler echocardiography and defined as a pulmonary artery systolic pressure above 35 mm Hg. **Results:** Three hundred fifty-three patients were recruited, of whom 94 (26.6%) had PH. Prevalence of PH increased with the decline of renal function: 21.6, 24.1, and 31.7% in stages 3, 4, and 5, respectively. Independent predictors of PH were age, estimated glomerular filtration rate (eGFR), history of cardiovascular (CV) events, the presence of an arteriovenous fistulae (AVF), and left ventricular (systolic and diastolic) dysfunction. Over a median follow-up of 22 months, 71 patients died (20%). After multivariate adjustment for age, gender, previous CV disease, diastolic and systolic dysfunction, PH remained as an independent predictor of all-cause mortality (hazards ratio [HR] 1.84, 95% CI 1.06–3.18, $p = 0.02$). One hundred patients (28%) had a new onset CV event. After adjustment for age, gender, previous

CV disease, systolic and diastolic dysfunction, PH maintains its independent association with CV events (HR 2.77, 95% CI 2.00–3.25, $p < 0.001$). **Conclusions:** PH prevalence rises as kidney function declines. Main determinants of PH are age, eGFR, previous CV disease, the presence of an AVF and left ventricular systolic or diastolic dysfunction. PH is an independent predictor of all-cause mortality and CV events.

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Introduction

In recent years, pulmonary hypertension (PH) in chronic kidney disease (CKD) patients is gaining interest because of its apparent high prevalence and its significant role in the outcome, principally in patients undergoing hemodialysis (HD) [1–3]. This condition usually remains asymptomatic and sometimes is misdiagnosed over a period of time until right ventricular dysfunction begins to manifest by worsening fatigue, dyspnea and syncope [4]. Recent studies suggest a higher prevalence of this entity in stage 5 non-dialysis dependent CKD patients [5, 6], HD patients [2, 7, 8] and peritoneal dialysis patients [9, 10] compared to healthy individuals. A recently published paper has included stages 1–4 CKD patients and evaluated the outcomes [11].

The gold standard for the diagnostic of PH is right heart catheterization (RHC) [4, 12]. Based on this procedure, PH is defined as a mean pulmonary arterial pressure above 25 mm Hg at rest [12]. RHC is an invasive, costly, risky and poorly accessible test, so transthoracic echocardiography is recommended for PH screening [13]. A good correlation has been found between both techniques [14, 15]. Although it is possible to estimate the mean pulmonary arterial pressure by 2D Doppler echocardiography, most studies often report the pulmonary artery systolic pressure (PASP) because of its accuracy [16, 17].

The aims of this study are to analyze the prevalence of PH in CKD patients and to elucidate the risk factors associated with PH and its prognosis value on mortality and cardiovascular (CV) events.

Methods

Patients

We conducted a prospective study, including stages 3–5 non-dialysis-dependent CKD patients from a single center in Madrid. CKD was defined and evaluated according to the Kidney Disease Outcomes Quality Initiative guidelines and using the Modification of Diet in Renal Disease equation [18]. Inclusion criteria were age ≥ 18 years, CKD stages 3–5 non-dialysis dependent, outpatient follow-up for at least 3 months, clinical stability (defined as no need for hospitalization or emergency care within 3 months prior to the inclusion). Exclusion criteria were clinical instability, inability to understand the study or rejection to personal data record and processing, poor echocardiography quality or PASP not correctly reported. All procedures were performed according to the Helsinki Declaration and its revisions. All patients gave consent for participation in the study and data processing. Demographic and clinical data on parameters such as age, gender, etiology of CKD (identified by clinical features and confirmed primarily by biopsy), diabetes mellitus, hypertension (as defined by the Eighth Report of the Joint National Committee [19]), history of previous CV disease including congestive heart failure (CHF), myocardial infarction, peripheral vascular disease, and stroke were collected.

Laboratory Tests

Laboratory parameters were routine tests, inflammation and nutrition parameters including albumin, high sensitivity C-reactive protein (hs-CRP), and cardiac biomarkers including amino terminal fragment of brain natriuretic peptide (NT-pro-BNP), high sensitivity T troponin (hs-TnT) and MB isoenzyme of creatine phosphokinase. All measurements were performed according to standard methods.

Echocardiographic Measurements

We performed a two-dimensional, M-mode and Doppler echocardiogram in the outpatient setting. The estimation of PASP by echocardiography is based on the modified Bernoulli equation as follows [20]: $PASP = 4 \times (TRV)^2 + RAP$. Where TRV is the maximum tricuspid regurgitation jet speed and RAP is the right atrium

pressure, which is estimated by inferior vena cava diameter according to the recommendations of the American Society of Echocardiography [21]. The upper normal limit is usually set between 30 and 35 mm Hg on the basis of a large population study [22]. PH was defined as a PASP value above 35 mm Hg. We considered severe PH when PASP was above 55 mm Hg. Systolic dysfunction was defined as left ventricular ejection fraction below 45% and diastolic dysfunction according to the echocardiographic parameters of the American Heart Association guidelines [23, 24]. We defined left ventricular hypertrophy as a left ventricular mass index above 130 g/m² (males) and 105 g/m² (women). The left ventricular mass was estimated using the Devereux formula [25].

Follow-Up and Outcomes Definitions

During a median follow-up period of 22 (3–49) months, new onset CV events were recorded. These events included ischemic or hemorrhagic cerebrovascular accident, myocardial infarction (diagnosed by cardiac marker elevation and electrocardiography), CHF and peripheral vascular events. We also recorded all-cause mortality during the follow-up period.

Statistical Analyses

All variables were analyzed using a Kolmogorov–Smirnov test to classify them as normally or non-normally distributed. Values were given as mean (SD) or median (interquartile range). Categorical data were compared using a chi-square test, while continuous variables were compared using a Student's *t* test or a Mann–Whitney U test. The mean PASP and PH prevalence between CKD stages was compared by using an analysis of variance. Univariate analysis was performed using logistic regression to assess factors associated with PH. The prognosis value of PH for predicting the study outcomes was assessed by the Kaplan–Meier analysis (survival curves were compared using a log-rank test) and Cox regression. In multivariate Cox models, we included all variables that showed significant association to the study outcomes at univariate Cox analyses. The models also included those considered confounders factors. All statistical analyses were performed with the SPSS 20.0® statistical package (SPSS, Inc., Chicago, IL, USA). Differences were considered statistically significant when *p* value was < 0.05 .

Results

PH and Baseline Data

The initial screening included 531 patients, of which 159 were excluded because PASP not correctly reported and also because of the absence of tricuspid regurgitation or poor acoustic window. The final study analysis was performed in 353 patients. The characteristics of this population are described in Table 1. Thirty-seven (10.5%) were in CKD stage 3, 187 (53%) in stage 4 and 129 (36.5%) in stage 5 non-dialysis dependent. The prevalence of PH was 26.6% (94 patients) and 6.5% of the population presented severe PH (PASP > 55 mm Hg). The mean PASP in the whole group was 28 ± 12.4 mm Hg, while in the PH group it was 46 ± 10.8 mm Hg. The prevalence of PH in-

Table 1. Clinical characteristics of the study population. Patients divided based on the presence of PH

	All	PH (present)	PH (absent)	<i>p</i> value
Patients	353 (100)	94 (26.6)	259 (73.4)	
Gender, male	193 (54.7)	49 (52.1)	144 (55.5)	0.6
Age, years	67±13	72±11	64±14	<0.001
Body mass index, kg/m ²	27.2±4.2	27.1±4.6	27.4±4.2	0.3
Hypertension	230 (65.1)	67 (71.2)	163 (63)	0.09
Diabetes mellitus	154 (43.6)	44 (46.8)	110 (42.5)	0.08
Chronic obstructive pulmonary disease	19 (5.4)	7 (6.6)	12 (4.6)	0.06
Obstructive sleep apnea	12 (3.4)	4 (4.2)	8 (3.1)	0.07
Etiology of ESKD				
Diabetes mellitus	82 (23.2)	22 (24.4)	60 (23.1)	0.3
Hypertension	90 (25.5)	23 (24.5)	67 (25.8)	0.4
Glomerulonephritis	76 (21.5)	19 (20.2)	57 (22)	0.3
Interstitial	40 (11.3)	10 (10.6)	30 (11.6)	0.3
APKD	25 (7.1)	6 (6.3)	19 (7.3)	0.4
Other	43 (12.2)	10 (10.6)	33 (12.7)	0.1
Estimated GFR, mL/min/1.73 m ²	18.9±8.1	15.1±9.1	21.3±8.8	0.04
Systolic blood pressure, mm Hg	141±19	140±18	142±18	0.4
Diastolic blood pressure, mm Hg	82±16	80±15	83±17	0.4
History of smoking				
Current	65 (18.4)	18 (19.1)	47 (18.1)	0.2
Past	87 (24.6)	27 (28.7)	60 (23.1)	0.09
Previous CV disease	95 (26.9)	33 (35.1)	62 (23.9)	0.001
Albumin, g/dL	4.3±0.2	4.1±0.3	4.4±0.2	0.7
C-reactive protein, mg/dL	0.7 (0.24–0.98)	1.2 (0.6–2.1)	0.6 (0.24–1.1)	0.04
NT-Pro-BNP, ng/L	45 (28–200)	209 (98–457)	33 (28–38)	<0.001
Hs-TnT, ng/L	50 (10–128)	64 (12–152)	40 (10–98)	0.001
Calcium, mg/dL	9.4±0.6	9.5±0.6	9.4±0.6	0.4
Phosphorus, mg/dL	4.6±0.9	5.5±0.8	4.4±0.7	0.04
Parathyroid hormone, mg/dL	120 (85–150)	156 (82–325)	98 (72–125)	0.001
Hemoglobin, g/dL	12.8±0.4	13.1±0.5	12.5±0.3	0.06
Arteriovenous fistulae	8 (2.2)	4 (4.2)	4 (1.5)	0.04
Systolic dysfunction	74 (21)	30 (32)	44 (16.9)	<0.001
Diastolic dysfunction	69 (19.5)	28 (29.7)	41 (15.8)	0.01
Left ventricular hypertrophy	92 (26)	27 (28.7)	65 (25.1)	0.07
Medications				
Anti-hypertensive	210 (59.4)	57 (60.6)	153 (59)	0.3
Antiaggregant	97 (27.4)	28 (29.7)	69 (26.6)	0.06
Epoetin	36 (13.5)	14 (14.8)	32 (12.3)	0.09

Data are given as mean ± SD, median (interquartile range) or numbers and percent frequency as appropriate.

Bold values in this table represent those that reached statistical significance.

ESKD, end-stage kidney disease; GFR, glomerular filtration rate; CV, cardiovascular; PH, pulmonary hypertension.

creases with the severity of CKD as seen in Table 2. Data analysis according to the presence or absence of PH showed that patients with PH were significantly older, with worse kidney function, higher hs-CRP, NtProBNP, hs-TnT and PTH levels. They were more frequently affected by previous CV disease. Systolic and diastolic dysfunctions were more frequent among patients with PH. All these differences are detailed in Table 1. Independent predictors of PH were age, estimated glomerular filtra-

tion rate (eGFR), history of CV events, presence of an arteriovenous fistulae (AVF), systolic and diastolic dysfunction as shown in Table 3.

PH and Risk of Death

During a median follow-up period of 22 (3–49) months, 71 patients died (20%), 27 in the non-PH group (16.9%) and 44 in the PH group (28.7%; *p* < 0.001). The main causes of death were CV (44.1%), followed by in-

Table 2. PH at different CKD stages

	All	Stage 3	Stage 4	Stage 5	<i>p</i> value
Patients	353 (100)	37 (10.5)	187 (53)	129 (36.5)	
PH prevalence	94 (26.6)	8 (21.6)	45 (24.1)	41 (31.7)	0.01
Mild PH: 35–55 mm Hg	71 (20.1)	7 (18.9)	33 (17.6)	31 (24)	0.01
Severe PH: >55 mm Hg	23 (6.5)	1 (2.7)	12 (6.5)	10 (7.7)	0.01
PASP, mm Hg	28±12	27±11	28±12	29±13	0.4
Mean eGFR, mL/min/1.73 m ²	18.9±8.1	43±6	23±3	9±2	0.01

Data are expressed as mean ± SD, or percent frequency as appropriate.

eGFR, estimated glomerular filtration rate; PH, pulmonary hypertension; PASP, pulmonary artery systolic pressure.

Table 3. Logistic regression analyses for variables associated with PH

	Unadjusted		Adjusted ^a	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (1 year)	1.03 (1.01–1.04)	<0.001	1.05 (1.01–1.08)	0.03
Estimated GFR (1 mL/min/m ²)	1.02 (1.01–1.04)	0.04	1.04 (1.02–1.08)	0.04
Previous CV disease	4.26 (1.06–11.24)	0.01	2.39 (1.94–2.39)	0.01
C-reactive protein (1 µg/dL)	1.09 (1.05–1.88)	0.04	1.01 (0.89–1.23)	0.06
Parathyroid hormone (1 mg/dL)	1.07 (1.05–2.01)	0.01	1.01 (0.79–1.86)	0.08
Arteriovenous fistulae	2.45 (1.86–3.12)	0.04	2.01 (1.51–2.10)	0.02
Systolic dysfunction	3.14 (2.85–3.55)	<0.001	3.07 (1.75–3.56)	0.01
Diastolic dysfunction	2.96 (2.69–3.51)	0.01	2.28 (1.29–2.81)	0.02

^a Multivariate model included all variables that were associated with PH at univariate analyses.

GFR, glomerular filtration rate; CV, cardiovascular.

fections (26.1%) and malignancy (20%). The relative risk of mortality was higher in patients with PH (hazards ratio [HR] 3.14, 95% CI 1.53–4.95, $p \leq 0.001$). In a Kaplan–Meier survival analysis, the risk of all-cause mortality is higher in patients with PH (Fig. 1). In the multivariate Cox model, PH remained as an independent predictor. Apart from PH, the independent variables increasing the risk of mortality were age, previous CV disease, systolic and diastolic dysfunction, as shown in Table 4.

CV Events

During the follow-up, it was found that there was new onset of CV events in 100 patients (28%) – 45 (47.8%) events in the PH group and 55 (21.2%) in the non-PH group ($p < 0.001$). The most common CV event was heart failure (24.8%) followed by stroke (20.2%) and cardiac arrest (12.4%). The Kaplan–Meier estimation of CV events, shown in Figure 2, demonstrate a higher risk of CV events among patients with PH. Again, the independently pre-

dictive value of PH for CV events was confirmed by the multivariate Cox model (HR 2.52, 95% CI 1.96–2.56, $p = 0.01$) as shown in Table 4.

Discussion

Our study supported the results of previous investigators who found that the prevalence among CKD patients was high. Moreover, we confirm that this prevalence rises as the kidney function declines. The main predictors of PH in CKD patients stages 3–5 are, age, eGFR, history of CV events, the presence of AVF, systolic and diastolic dysfunction. We also found a worse prognosis of this population group when diagnosed with PH, this entity being an independent predictor of mortality and CV events.

Two large population-based studies had analyzed the prevalence of PH in general population and found that it was between 5 and 9.1% [22, 26]. Our study showed a prev-

Fig. 1. Kaplan–Meier cumulative survival curve for all-cause mortality.

Fig. 2. Kaplan–Meier cumulative survival curve for CV events.

Table 4. Crude and adjusted Cox regression analyses for all-cause mortality and CV events

	Unadjusted		Adjusted ^a	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
<i>CV events</i>				
Age, years	1.04 (1.01–1.06)	0.01	1.03 (1.01–1.04)	0.04
Previous CV disease	4.96 (4.03–13.08)	<0.001	4.05 (2.17–7.13)	<0.001
Diabetes mellitus	1.98 (1.25–2.76)	0.01	1.23 (1.12–1.65)	0.04
PH	3.02 (1.66–5.50)	<0.001	2.52 (1.95–5.56)	0.01
Diastolic dysfunction	4.41 (2.37–7.25)	<0.001	1.82 (1.21–2.95)	0.02
Systolic dysfunction	2.25 (1.26–4.00)	0.04	1.08 (0.98–2.92)	0.06
<i>All cause mortality</i>				
Age, years	1.02 (1.00–1.04)	0.03	1.16 (1.03–1.14)	0.03
Previous CV disease	2.09 (1.38–3.09)	<0.001	1.52 (1.05–2.53)	0.02
C-reactive protein	1.23 (1.09–1.35)	<0.001	1.09 (0.98–1.10)	0.06
PH	3.14 (1.53–4.95)	<0.001	1.74 (1.16–3.08)	0.02
Diastolic dysfunction	3.25 (2.13–5.89)	<0.001	1.71 (1.09–1.94)	0.02
Systolic dysfunction	2.15 (1.25–2.60)	0.01	1.22 (1.12–1.29)	0.03

^a Multivariate model included all variables that were associated with study outcomes at univariate analyses.

alence of 26.6% in patients with CKD stages 3–5 non dialysis dependent. Similar findings were reported by a recent study that included 468 CKD patients where the prevalence was 23% [11]. This increased prevalence could be explained by multiple factors. The main determinants of pul-

monary arterial pressure are cardiac output, pulmonary vascular resistance and pulmonary capillary wedge pressure [27]; all these factors can be altered at a variable extent in CKD patients. Thus, an increase in cardiac output due to hyperdynamic circulation secondary to AVF, anemia

[28] and volume overload affects some of the CKD patients [29]. Our study shows a significantly higher prevalence of AVF in PH patients as well as a higher concentration of Nt-Pro-BNP this fact could reflect a high prevalence of left ventricular dysfunction in this population but also, could be a volume status marker. However we did not found any difference in the hemoglobin levels or epoetin usage between both groups of patients.

Pulmonary vascular resistance can be affected by 3 factors: first, endothelial dysfunction and production of vasoactive molecules from the endothelium in uremic milieu [30, 31]. Among other molecules, asymmetric dimethylarginine (ADMA) and endothelin-1, are found in high concentrations in CKD patients [32, 33]; ADMA is an endogenous inhibitor of vasodilator effect of nitric oxide while endothelin-1 is a potent vasoconstrictor. Both molecules may play an important role increasing systemic and pulmonary vascular resistance. In this study, we have not measured these laboratory parameters. Second, vascular calcification in CKD is not always restricted to systemic circulation; it can also affect the pulmonary tree [34]. Animal studies suggest that prolonged exposure to PTH effects induces pulmonary vascular calcification, which is manifested by decreased diffusing capacity and vascular compliance, alterations that can reverse after parathyroidectomy [35]. However, in our study, we did not find differences in calcium, phosphorus or PTH concentration between both groups. Similar findings were reported by Amin et al. [36] in 15 HD patients, in which they also analyzed the degree of pulmonary vascular calcification by technetium⁹⁹ diphosphate-marked scintigraphy; they however did not find significant differences between patients with and without PH.

Finally, pulmonary capillary wedge pressure is mainly determined by the filling pressure in the left heart chambers, which is influenced by systolic and diastolic dysfunction, both conditions being highly prevalent among CKD patients [37]. In our study, we found a higher prevalence of systolic and diastolic dysfunction among PH patients, highlighting the main role that this entity may have in the development of PH.

Recent studies have shown that end-stage renal disease patients with PH have worse prognosis than patients without PH [2, 3, 6, 38, 39]. Our study in non-dialysis-dependent CKD patients confirms that the presence of PH is an independent predictor of CV events and mortality, besides being a direct consequence of other diseases that are also predictors of mortality (systolic dysfunction, diastolic dysfunction, etc.). After the statistical adjustment for these variables, PH maintains its predictive val-

ue of mortality and morbidity; therefore, it appears that PH itself, regardless of etiology, plays an important role in the prognosis of CKD patients. In addition to the mechanical effect of chronic increased pressure in the pulmonary vascular tree on right ventricular function, there is evidence that diffusion of carbon dioxide is significantly lower in HD patients, probably as a result of some degree of subclinical pulmonary edema. Indeed, ultrafiltration can improve the ventilation/perfusion ratio [40].

Our study has some limitations. First, we have only estimated the PASP by echocardiography, instead of measuring it directly by RHC. Because of its invasive nature, as far as we know to date, only one study has been reported in which the PASP was measured using RHC [5]. Most of studies use the estimate PASP by transthoracic echocardiography because of its noninvasive nature and the good correlation with RHC [14, 15]. Second, no other information about volume status or body composition analysis by bioimpedance was collected.

We conclude that PH is a common finding in CKD, and its prevalence becomes higher as renal disease progresses. The main predictors of PH are, age, loss of renal function, history of CV events, the presence of an AVF and left ventricular dysfunction. PH is also a valuable predictor of mortality and CV events. Doppler echocardiography is a useful tool to identify patients at risk. Further studies are needed to assess whether the early intervention on risk factors (e.g. fluid overload) could improve patients' outcomes.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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