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Original Research Article

A Hospital Based Observational Cross Section Study of Pulmonary Hypertension in Patients with Chronic Kidney Disease

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Abstract

Aim: The aim of the present study was to assess the occurrence of pulmonary arterial hypertension in chronic kidney disease and to study the risk factors for development of pulmonary arterial hypertension (PH) in these patients.

Methods: This was an observational cross sectional study conducted on 200 patients of CKD (based on KDIGO 2012 criteria) attending Medicine OPD or admitted to the Nephrology wards in Patna Medical College and Hospital, Patna, Bihar, India for one year.

Results: Pulmonary hypertension was found in 120 patients (60%) of the study population. No significant association was seen between age, BMI, presence of diabetes and s.uric acid with presence of PH. Significant association was seen with systolic and diastolic blood pressure with PH. Significant association was also seen with severity of CKD & PH. Presence of hemodialysis and dialysis duration were significantly associated with PH. Of 120 patients with PH, 45 patients (37.50%) had mild PH, 65 patients (54.16%) had moderate PH and 10 patients (8.34%) had severe PH.

Conclusion: We concluded that pulmonary arterial hypertension is significantly associated in patients of CKD and increase in severity of PAH occurs with deterioration of renal function in CKD cases. Anemia, duration of dialysis, hypertension, hyperparathyroidism, AV fistula, increased calcium phosphate product and left ventricular failure are risk factors for development of PAH.

Keywords: Pulmonary Arterial Hypertension, Chronic Kidney Disease, Risk Factors.

Introduction

The prevalence of chronic kidney disease (CKD) in the developed world is 13% [1] and is recognized as a condition that increases the risk of cardiovascular complications as well as kidney failure and other complications. End-stage kidney disease (ESKD) substantially increases the risk of death due to cardiovascular disease, and requires specialized health care. In this context, pulmonary hypertension (PH) has been reported in patients with ESKD maintained on long-term hemodialysis. Based on echocardiographic studies, the prevalence of PH in these patient populations is estimated to be around 17–56% [2-5], and PH is an independent predictor of mortality in such patients. [6,7] PH is a hemodynamic and pathophysiological state found in a range of clinical conditions and is characterized by an increase in mean pulmonary arterial pressure (mPAP ≥25 mmHg); precapillary PH is defined by the additional criterion of a pulmonary capillary wedge pressure (PCWP) ≥15 mmHg. [8]

Pulmonary hypertension (PH) is primarily a disease of the small arteries of the pulmonary vasculature, with progressive obliteration leading to the increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) that characterize the disease. [9] The increased PVR often leads to right ventricular failure associated with high mortality. [10] The mechanisms responsible for PH still remain incompletely understood. Many studies have shown that PH occurred frequently in patients with chronic kidney disease (CKD) and some of them have explored the relation between CKD and PH. [11,12] PH in patients with CKD may be induced and aggravated by left ventricular disorders and risk factors typical of CKD, including volume overload, an arteriovenous fistula, sleep-disordered breathing, exposure to dialysis membranes, endothelial dysfunction, vascular calcification and stiffening, and severe anemia. [11] Despite increased recognition of PH as an important contributor to

mortality among CKD patients, little is known about the etiology of PH in patients with CKD. [13] Epidemiologic and long-term outcome data are lacking on the impact of PH, particularly among patients with early stage CKD. [14,15] Potential mechanisms for the development of PH in patients with CKD include endothelial dysfunction, increased flow through arterio-venous shunts, exposure to dialysis membranes, and elevated left ventricular filling pressure. [14]

The aim of the present study was to assess the occurrence of pulmonary arterial hypertension in chronic kidney disease and to study the risk factors for development of pulmonary arterial hypertension in these patients.

Materials and Methods

This was an observational cross sectional study conducted on 200 patients of CKD (based on KDIGO 2012 criteria) attending Medicine OPD or admitted to the Nephrology wards in Patna Medical College and Hospital, Patna, Bihar, India. Each patient was subjected to detailed history and clinical examination and relevant investigations were done including CBC, KFT, random blood sugar, s. electrolytes, s. calcium, s. phosphorus, s. iPTH, s. uric acid, urine routine and microscopy, USG abdomen, Chest X-Ray, ECG and echocardiography. PAH (PH) was diagnosed on the basis of echocardiography with mean pulmonary arterial pressure (MPAP) of ≥25mmHg at rest was taken as diagnostic of pulmonary arterial hypertension. Pulmonary hypertension was classified as:

- Mild (25-40 mHg)
- Moderate (40-60 mmHg)
- Severe (>60 mmHg)

Inclusion Criteria

1. Patients of CKD in stage IV and stage V.
2. Age ≥18 years.

Exclusion Criteria

- Valvular heart disease
- Congenital heart diseases
- Chronic obstructive pulmonary disease
- Chronic parenchymal lung disease
- HIV-infected patients
- Chronic liver disease
- Connective tissue diseases
- Hypothyroidism and hyperthyroidism.
- Pregnancy
- Chronic thromboembolic disorders.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows:

Quantitative variables were compared using unpaired t-test/Mann- Whitney Test (when the data sets were not normally distributed) between CKD. Qualitative variables were compared using Chi-Square test / Fisher's exact test. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Table 1: Characteristics of patients with and without PH

Parameters	WithPH(n=120)	WithoutPH(n=80)	Pvalue
Age	32.24 ± 8.52	34.36 ± 8.55	0.255
BMI	23.57 ± 1.62	24.6 ± 1.60	0.316
SBP	146.4 ± 12.72	138.32 ± 12.12	<0.0001
DBP	85.65 ± 7.47	83.57 ± 6.34	0.0005
CKD stage 4	36	65	<0.0001
CKD stage 5	84	15	<0.0001
Presence of hemodialysis	96	46	0.0004
Hemodialysisduration(weeks)	10.12 ± 4.42	6.44 ± 3.47	0.0001
PresenceofAVF	40	0	0.006
Presence of diabetes	25	20	0.325
Hemoglobin	7.43 ± 0.63	8.42 ± 0.48	<0.0001
S. UricAcid	7.16 ± 0.75	7.08 ± 1.08	0.626
S. Calcium	7.45 ± 0.43	8.24 ± 0.32	<0.0001
S. Phosphate	6.79 ± 0.7	4.37 ± 0.43	<0.0001
CalciumPhosphateproduct	51.3 ± 3.86	35.58 ± 3.43	<0.0001
iPTH	396.21 ± 62.69	138.79 ± 36.28	<0.0001
LVEF%	35.77 ± 6.14	52.69 ± 5.6	<0.0001

Pulmonary hypertension was found in 120 patients (60%) of the study population. No significant association was seen between age, BMI, presence of diabetes and s. uric acid & presence of PH. Significant association was seen with systolic and diastolic blood pressure with PH. Significant association was also seen between severity of CKD & PH. Presence of hemodialysis and dialysis duration were significantly associated with PH. Significant association was also seen with presence of AVF and presence of PH. Low hemoglobin level was also significantly associated with PH. Low serum calcium, high serum phosphorus, increased calcium phosphate product and increased intact parathormone were also significantly associated with presence of PH. Patients with PH had lower LVEF%.

Table 2: Characteristics of patients with mild, moderate and severe PH

Parameters	MildPH(n=45)	ModeratePH(n=65)	SeverePH(n=10)	Pvalue
Age	34.54 ± 10	29 ± 6.44	43.47 ± 2.08	0.001
BMI	23.47 ± 1.52	24.48 ± 1.36	23.57 ± 3.14	0.010
SBP	142.08 ± 12.28	150.30 ± 8.62	147.3 ± 20.40	0.004
DBP	84.72 ± 7.03	87.33 ± 7.5	89 ± 9.56	0.223
CKD stage 4	32	8	0	<0.0001
CKD stage 5	13	57	10	<0.0001
Presence of Hemodialysis	25	55	10	0.068
Hemodialysisduration(weeks)	6.44 ± 1.74	13.47 ± 5.35	18.2 ± 1.88	<0.0001
PresenceofAVF	0	14	6	0.001
Presence of Diabetes	12	2	5	0.0003
Hemoglobin	7.53 ± 0.32	7.24 ± 0.52	6.84 ± 0.3	<0.0001
S. UricAcid	7.12 ± 1.02	6.74 ± 0.89	8.22 ± 0.62	0.071
S. Calcium	7.8 ± 0.52	7.30 ± 0.38	7.35 ± 0.72	0.077
S. Phosphate	6.84 ± 0.54	7.03 ± 0.2	7.18 ± 0.12	<0.0001
Calcium Phosphate Product	49.31 ± 3.4	51.59 ± 2.87	54.46 ± 4.20	<0.0001
iPTH	348.62 ± 54.46	426.74 ± 44.76	459.5 ± 9.31	<0.0001
LVEF%	38.32 ± 4.26	34.56 ± 6.04	36 ± 7.07	0.001

Of 120 patients with PH, 45 patients (37.50%) had mild PH, 65 patients (54.16%) had moderate PH and 10 patients (8.34%) had severe PH. High systolic blood pressure was found to be significantly associated with increased severity of PH. Also as the CKD stages progressed, severity of PH also increased significantly. Patients with increased duration of dialysis and patients with AVF had increased severity of PH. Low hemoglobin, increased serum phosphate, increased calcium phosphate product and increased intact parathormone were also found to be significantly associated with increased severity of PH. Also patients with low LVEF% had higher severity of PH.

Table 3: Multivariate logistic regression to find out independent significant risk factor of pulmonary hypertension

Variable	Beta coefficient	Standard error	R^2	P value	Odds ratio	Oddsratio Lower bound (95%)	Oddsratio Upperbound (95%)	
Systolic blood pressure (mmHg)	-0.024	0.053	0.655	0.945	0.840	1.080	94.19 %	
Diastolic blood pressure(mmHg)	0.044	0.100	0.632	1.058	0.890	1.276		
Dialysis duration(weeks)	-0.185	0.206	0.380	0.860	0.590	1.260		
Haemoglobin(gm/dL)	-1.150	1.585	0.450	0.326	0.018	7.376		
S.Calcium(mg/dL)	-14.270	9.752	0.135	0.000	0.000	124.350		
S.Phosphate(mg/dL)	-15.368	10.786	0.159	0.000	0.000	266.712		
Calcium Phosphateproduct	2.120	1.432	0.132	8.246	0.525	131.787		
Intact parathormone(pg/mL)	0.009	0.014	0.418	1.009	0.981	1.032		
LVEF%	-0.043	0.093	0.644	0.958	0.798	1.149		
CKDstage								

4				1			
5	1.555	1.936	0.447	4.763	0.083	219.139	

On performing multivariate logistic regression after adjusting for confounding factors, none of the factors was found to be an independent significant risk factor for pulmonary hypertension.

Discussion

Cardiovascular disease is the most common cause of morbidity and mortality in patients with chronic kidney disease (CKD). [16] The focus is usually on left ventricular failure causing increased morbidity and mortality in the patients of CKD whereas pulmonary arterial hypertension (PAH) is an overlooked cardiovascular complication of CKD, especially in end-stage renal disease (ESRD). Elevated pulmonary arterial pressure (PAP) can be observed secondary to heart, lung, or systemic disorders. PAH is defined as "a mean pulmonary artery pressure more than or equal to 25 mmHg at rest or 30 mmHg at exercise." [17] Navaneethan et al.reported an increased mortality in a cohort of PH patientswith CKD, [18] but did not investigate a population of CKDpatients for the presence of PH. The hemodynamic profilesof PH (pre-capillary PH versus post-capillary PH) in theCKD population have not been fully explored. Therefore,studies employing invasive hemodynamics are needed togain insight into the etiology of PH among CKD patients.Moreover, prior studies have lacked information aboutimportant co-morbidities and echo variables that may influencethe relationship between PH and CKD.

Pulmonary hypertension was found in 120 patients (60%) of the study population. No significant association was seen between age, BMI, presence of diabetes and s. uric acid with presence of PH. Significant association was seen with systolic and diastolic blood pressure with PH. Significant association was also seen with stages of CKD with PH. Presence of hemodialysis and dialysis duration were significantly associated with PH. Significant association was seen with presence of AVF and presence of PH. Low hemoglobin level was also significantly associated with PH. Low serum calcium, high serum phosphate, increased calcium phosphate product and increased intact parathormone were also significantly associated with presence of PH. Patients with PH had lower LVEF%. Similar results were observed by Zhang et al [19] where patients with higher BMI had severe PH. However in a study by K. Ramasubbu et al [20] patients with more severe PH had lower BMI. Although, obesity is risk factor for the development of cardiovascular disease, diabetes mellitus, hypertension, renal disease and metabolic abnormalities, the results of association of BMI with severity of PH are conflicting.

Of 120 patients with PH, 45 patients (37.50%) had mild PH, 65 patients (54.16%) had moderate PH and 10 patients (8.34%) had severe PH. High systolic blood pressure was found to be significantly associated with increased severity of PH. Also as the CKD stage progressed, severity of PH also increased significantly. Patients with increased duration of dialysis and patients with AVF had increased severity of PH. Low hemoglobin, increased serum phosphate, increased calcium phosphate product and increased intact parathormone were also found to be significantly associated with severity of PH. Also patients with low LVEF had more severe PH. In studies by Zhang et al [19] and K. Ramasubbu et al [20] no significant association was seen with either systolic blood pressure or diastolic blood pressure & severity of PH. Hence, although hypertension is associated with the presence of PH in CKD patients in most of the previous studies, no definitive association was seen with the severity of PH. On performing multivariate logistic regression after adjusting for confounding factors, none of the factors was found to be an independent significant risk factor for pulmonary hypertension. Our study also showed a significant association of increased phosphate, increased calcium phosphate product and increased iPTH with the severity of PH. In contrast, Zhang et al [19] in their study showed no such association between calcium, phosphate and calcium phosphate product values with severity of PH, however they noticed that iPTH values in severe PH was much higher compared to mild and moderate PH.

In dialysis patients, the prevalence of PH was much higher. In this study, patients with congenital heart failure and acute heart failure had been excluded. However subclinical heart failure was common in ESRD patients. The causes might include hypertension, Na and water overload, pleiotropic effects of uraemic toxins and myocardial ischaemia. These factors were more prevalent in patients with PH. Arteriovenous fistulae (AVF) are considered the gold standard for HD access. [21] They result in increased venous return with a concomitant increase in cardiac output and also lead to decreased systemic vascular resistances. [22] In a study of patientsreceiving PD, LV mass index alongside low serum albumin and fluid overload, were predictors of PH in a multivariate model. [23]

Conclusion

We concluded that pulmonary arterial hypertension is significantly associated in patients of CKD and increase in severity of PH occurs with deterioration

of renal function in CKD cases. Anemia, duration of dialysis, hypertension, hyperparathyroidism, AV fistula, increased calcium phosphate product and left ventricular failure are risk factors for development of PAH. Treatment of these risk factors can decrease the progress as well as severity of PAH, thereby decreasing the morbidity and mortality in CKD patients.

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