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Original Research Article

A Hospital-Based Assessment of the Prevalence of Pulmonary Hypertension in Patients with Chronic Kidney Disease

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Abstract

Aim: The aim of this study was to analyze the prevalence of PH in patients with CKD, its severity in different stages of CKD and risk factors for it.

Methods: The present study was conducted at Department of Nephrology, Indira Gandhi institute of medical Sciences (IGIMS), Patna, Bihar, India for 18 months and 100 patients were included in the study. Selected patients were informed about objectives of the study, and informed consent was taken from the patient or their guardian. Information was collected using a preformed proforma from each patient.

Results: The mean age of the study population was 44.53 ± 14.63 years. There were 70 males and 30 females in the present study. There were 90 patients in stage 5 CKD disease followed by 7 patients in stage 4 and 3 patients in stage 3. Heart failure with reduced EF (HFrEF) was present in 26 (26%) of 100 patients. Among the patients with LV systolic dysfunction, majority had mild dysfunction. The prevalence of heart failure with preserved EF (HFpEF,) was 85 (85%) of 100 patients at first ECHO, increased further at follow-up ECHO. Among patients with CKD stage 3 and 4, majority had mild PH, but in stage 5, it was predominantly moderate PH (25 of 92 [27.17%]) patients. This indicates that PH increased in severity with progression of CKD, although this was not statistically significant, since there were few patients in stage 3 and stage 4.

Conclusion: PH is a common complication in CKD patients with prevalence of 43.5%–50%. Left-sided heart failure, anemia, fluid retention, and increased calcium phosphate product are the risk factors for developing PH.

Keywords: Calcium Phosphate Product, Chronic Kidney Disease, Ejection Fraction, Pulmonary Hypertension.

Introduction

Pulmonary hypertension (PH) is a common co-morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease. [1–3] More importantly, the presence of PH is associated with increased risk of hospitalization and mortality in patients with CKD. [3,4] Despite its prognostic significance, the true prevalence of PH in CKD is unclear. The majority of prior

studies reporting the prevalence of PH in patients with CKD have defined PH based on echocardiography,[1–3] which is frequently inaccurate.[5] In addition, the pathogenesis of PH in CKD are not well defined. Many different mechanisms may play a role. [6]

Chronic kidney disease (CKD) is a common health problem worldwide. Cardiovascular disease is the most common cause of morbidity and mortality in CKD. [7] Pulmonary hypertension (PH) is an overlooked cardiovascular complication of CKD, especially in end‐stage renal disease (ESRD). The prevalence of PH in patients with ESRD ranges from 27% to 58%.[8] Patients with advanced CKD have a prevalence of PH that is lesser than that in patients with ESRD, ranging from 8% to 39%.[9,10] PH is an independent predictor of increased mortality in patients with CKD.[8,9]

PH is defined as "a mean pulmonary artery pressure more than or equal to 25 mmHg at rest or 30 mmHg at exercise." The pathogenesis of PH in CKD is not fully elucidated. [8] It is considered to be due to interaction of multiple aspects of altered cardiovascular physiology. Myocardial dysfunction leading to elevated left ventricular filling pressure and pulmonary venous hypertension is the predominant cause of PH in CKD.[9,11,12] The other factors implicated are increased cardiac output (CO),[8,9] increased pulmonary blood flow due to shunting across arteriovenous fistula (AVF) [12,13] volume overload, anemia, exposure to dialysis membranes,12 endothelial dysfunction leading to pulmonary vasoconstriction, decreased compliance of pulmonary vasculature, vascular calcification and stiffening,[12] increased thromboxane B2, and pro‐brain natriuretic peptide.[10]

The aim of this study was to analyze the prevalence of PH in patients with CKD, its severity in different stages of CKD and risk factors for it.

Materials and Methods

The present study was conducted at Department of Nephrology, Indira Gandhi institute of medical Sciences (IGIMS), Patna, Bihar, India for 18 months and 100 patients were included in the study. Selected patients were informed about objectives of the study, and informed consent was taken from the patient or their guardian. Information was collected using a preformed proforma from each patient.

Inclusion criteria

- Newly diagnosed cases of CKD based on Kidney.
- Disease Improving Global Outcome 2012 criteria, including CKD patients on hemodialysis.
- Age ≥18 years.

Exclusion criteria

- Those not willing to participate in the study.
- Age <18 years.
- Valvular heart diseases.
- Congenital heart diseases.
- Pulmonary obstructive and restrictive diseases.
- HIV‐infected patients.
- Chronic liver disease.
- Connective tissue diseases.
- Hypothyroidism and hyperthyroidism

The history was elicited with special reference to symptoms of CKD, congestive heart failure, PH, risk factor for developing CKD, comorbid conditions, duration of diagnosis of CKD, and HD. Clinical signs of CKD, heart failure, and PH were assessed. Each case underwent relevant investigations. Staging of CKD was done based on estimated glomerular filtration rate (eGFR) estimated by Modification of Diet in Renal Disease formula. Electrocardiogram (ECG) was done to look for features of PH, right ventricular (RV) strain pattern, left ventricular (LV) strain pattern, and IHD. Echocardiography was done in all patients at the beginning of the study, 3 months,

and 6 months. Pulmonary artery systolic pressure (PASP) was calculated using TR jet velocity in Doppler echocardiography and applying Bernoulli equation. A PASP value of ≥35 mmHg at rest was taken to be suggestive of PH. Echocardiography was also used to assess the LV hypertrophy, dilatation, chamber size, LV systolic function and diastolic function, LV ejection fraction (EF), regional wall motion abnormality, and pericardial effusion. Comparison was made between CKD patients with presence and absence of PH.

Statistical analysis

Descriptive and inferential statistical analysis had been carried out in the study. The continuous variables such as age, blood pressure (BP), and EF were expressed in terms of mean ± standard deviation (SD). The categorical measurements were expressed in number (percentage). Significance was assessed at 5% level of significance ($P < 0.05$).

Results

Table 1: General characteristics of patients

Variables	N
Age (years)	
Mean±SD	43.53±14.63
Range	18-80
Gender	
Male	70 (70)
Female	30 (30)
Hypertension	
Systolic	75 (75)
Diastolic	60 (60)
Diabetes Mellitus	30 (30)
Anemia	95 (95)
CKD stages	
Stage 3	3 (3)
Stage 4	7 (7)
Stage 5	90 (90)
Duration of CKD (weeks)	
Mean±SD	24.76±54.5
Range	0-416
Duration of dialysis (weeks)	
Mean±SD	40.88±68.27
Range	0-416
Dry weight attained, n (%)	55 (55)

The mean age of the study population was 44.53 ± 14.63 years. There were 70 males and 30 females in the present study. There were 90 patients in stage 5 CKD disease followed by 7 patients in stage 4 and 3 patients in stage 3.

Table 2: Echocardiographic findings of patients

Echo findings	At beginning (n=100), n (%)	At 3 month (n=75), n (%)	At 6 month (n=60), n (%)
LV hypertrophy	15 (15)	15 (20)	10 (16.66)
HFrEF	26 (26)	20 (26.66)	15 (25)
Mild (EF: 45%-54%)	20 (20)	14 (18.66)	9 (15)
Moderate (EF: 30%-44%)	6 (6)	4 (5.33)	4 (6.66)
Severe (EF: <30%)	0	1 (1.33)	2 (3.33)
HFpEF	85 (85)	65 (86.66)	55 (91.6)
PH	45 (45)	38 (50.66)	30 (50)
Mild (PASP: 35-49 mmHg)	20 (20)	18 (21.7)	11 (18.3)
Moderate (PASP: 50-69 mmHg)	22 (22)	20 (26.66)	12 (20)
Severe (PASP: ≥70 mmHg)	2 (2)	2 (2.66)	6 (10)
Right ventricular dilatation	40 (40)	30 (40)	27 (45)
Right atrial dilatation	40 (40)	30 (40)	27 (45)
Pericardial effusion	15 (15)	8 (10.66)	5 (8.33)

Heart failure with reduced EF (HFrEF) was present in 26 (26%) of 100 patients. Among the patients with LV systolic dysfunction, majority had mild dysfunction. The prevalence of heart failure with preserved EF (HFpEF,) was 85 (85%) of 100 patients at first ECHO, increased further at follow‑up ECHO.

Table 3: Pulmonary hypertension in different stage of chronic kidney disease

PH grades	Stage of CKD			Total
	Stage 3	Stage 4	Stage 5	
Absent	2	3	50	55
Mild	1	2	12	15
Moderate	0	0	25	25
Severe	0	0	5	5
Total	3	5	92	100

Among patients with CKD stage 3 and 4, majority had mild PH, but in stage 5, it was predominantly moderate PH (25 of 92 [27.17%]) patients. This indicates that PH increased in severity with progression of CKD, although this was not statistically significant, since there were few patients in stage 3 and stage 4

Table 4: Comparison of parameters between pulmonary hypertension and nonpulmonary hypertension group

Parameters	PH		Total (n=100), n (%)	P- value
	Present n=45	Absent n=55		
Clinical features				
Dyspnea	38	42	80 (80)	0.018
Fatigue	28	30	60 (60)	0.070
Chest pain	14	11	25 (25)	0.150
Pedal edema	39	41	80 (80)	0.220
Pallor	45	50	95 (95)	0.018
Parasternal heave	6	2	8 (8)	0.075
Loud p2	25	10	35 (35)	<0.001
TR murmur	8	4	12 (12)	0.085

Basal crepts	18	17	35 (35)	0.310
Ascites	13	9	22 (22)	0.010
Biochemical parameters				
Anemia	45	50	95 (95)	0.250
Serum protein ≤6 g/dl	12	14	26 (26)	0.270
Serum albumin <4 g/dl	22	26	48 (48)	0.820
Calcium × phosphate product ≥50	14	8	22 (22)	0.05
ECG				
Right atrial abnormality	1	0	1 (1)	0.430
Left ventricle strain	13	12	25 (25)	0.220
IHD	1	1	2 (2)	1.000
Right ventricular strain	3	1	4 (4)	0.196
ECHO				
LV hypertrophy	9	9	18 (18)	0.543
HFrEF	17	3	20 (20)	<0.001
HFpEF	40	45	85 (85)	0.006
Right ventricular dilatation	40	0	40 (40)	<0.001
Right atrial dilatation	40	0	40 (40)	<0.001
Pericardial effusion	13	2	15 (15)	<0.001

The prevalence of clinical features of PH dyspnea, loud P2, and ascites were significantly higher among the patients with PH compared to those without PH. There was no significant difference in various ECG findings between the patients with PH and without PH. HFrEF, HFpEF, and pericardial effusion were significantly higher among the patients with PH, compared to those without PH.

Discussion

Chronic kidney disease (CKD) is common in the USA, affecting over 25 million people. [14] Pulmonary hypertension (PH) and CKD often co-exist [1,15,16]and prior studies suggest that PH is associated with increased mortality in patients with CKD. [1,16] Moreover, the prevalence of PH increases across CKD stages in a dose-response manner, an observation that suggests a potential direct relationship. [17] PH in CKD can occur through multiple mechanisms, including PH of WHO Group 1–5 (pulmonary arterial hypertension, left‐sided heart disease, chronic pulmonary disease and hypoxia, chronic thromboembolic disease, and unexplained PH, respectively).[8]The prevalence of heart failure in patients with CKD is 30%–40%. [18,19] This is the most important mechanism contributing to PH (WHO Group 2) in CKD patients and has been extensively evaluated in many studies.[8,9] In our study, HFrEF was present in 20%. Its prevalence among the patients with and without PH was 17 and 3, respectively ($P < 0.001$). The mean EF among the patients with PH was significantly lower, compared to those without PH. This is consistent with the study by Kumbar et al. [20] and Fabbian et al. [13] HFpEF was present in 85.2% of cases. The prevalence of HFpEF was significantly higher among the patients with PH, compared to those without PH ($P = 0.006$). This is consistent with the study by Abdelwhab et al. [10]

HFrEF and HFpEF were persistent despite being on HD in our study, thus contributing to the development of elevated LV filling pressure and pulmonary venous hypertension. Although HD corrects volume overload and removes the toxic metabolites, it did not have a significant impact on LV function and PASP. LV failure is a multifactorial process in patients with CKD. It is caused

by chronic volume overload, elevated mean arterial pressure, uremia‑mediated cardiac myocyte dysregulation, anemia‑mediated hypoxemic stress, and impairment in cardiac function by microvascular and macrovascular coronary artery disease. [21] Hypertension and diabetes mellitus, which are two dominant causes of CKD, trigger LV diastolic dysfunction, an alteration bound to increase pulmonary venous and arterial pressure.[22] However, in our study, there was no significant difference in prevalence of hypertension and diabetes mellitus between the two groups. Persistent elevation of the PCWP owing to impaired diastolic relaxation leads to vascular remodeling with thickening of the pulmonary capillary endothelial basal lamina and proliferation of connective tissue surrounding the alveoli. A study of 76 ESRD by Abdelwhab et al. showed that patients with diastolic dysfunction have an odds ratio of 21.9 for developing PH. [10]

Lower diastolic BP (DBP) was found to be associated with PH in a study by Kumbar et al. [20] However, in our study, there was no significant difference in either DBP or systolic BP between the patients with and without PH. Anemia is a common manifestation of CKD and important risk factor for developing PH found in our study. The mean Hb was significantly lower among PH group compared to non‑PH group, thus implicating the role of anemia in PH. This is consistent with the study by Yigla et al. [9] and Etemadi et al. [23] In our study, Percentage prevalence of higher calcium phosphate product was significantly greater among those with PH, compared to those without PH. This is consistent with the study by Kumbar et al.20 Increased calcium phosphate product predisposes to pulmonary vascular calcification, leading to PH. [8,20] In our study, interdialytic weight gain and CVP were significantly higher among the patients with PH, compared to those without PH This is consistent with the study by Fabbian et al. [13] This suggests fluid retention to be a contributing factor for developing PH.

In our study, the mean dialysis duration was found to be higher among the patients with PH than those without PH. This is consistent with the study by Fabbian et al. [13] The pathogenic mechanisms proposed for PH in CKD patients on hemodialysis are AVF‑induced, increased CO, which cannot be accommodated by pulmonary circulation. In addition, pulmonary vessels show signs of endothelial dysfunction resulting in dysregulation of vascular tone due to an imbalance between vasodilators, such as prostacyclins and nitric oxide (NO), and vasoconstrictors, such as endothelin‑1, plasma asymmetric dimethylarginine, and thromboxane B2, and local as well as systemic inflammation. [24] It is also believed that microbubbles escaping from the dialysis circuit can trigger vasoconstriction and vascular sclerosis. [10]

Conclusion

Our study concludes that substantial number of the patients with CKD develops PH. HFrEF and HFpEF are the strongest risk factors. Hence, PH in CKD is predominantly WHO group 2. Thus, PH can be considered as a reflection of cardiorenal syndrome type 4. The other factors contributing to it are anemia, volume overload, and increased calcium phosphate product. PH may be a cause for refractory dyspnea, edema, and ascites in patients with CKD. Long‑standing PH is associated with increased morbidity and mortality. Estimation and follow‑up of PASP by Doppler echocardiography may be indicated in all the patients with CKD, especially ESRD.

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