Original Research Article

# Clinical study of pulmonary hypertension in various stages of chronic kidney disease at a tertiary care center

Vijay Kumar[1], Eshan Sharma[2*]

{[1]Associate Professor, Department of Nephrology} {[2]Associate Professor, Department of General Medicine} NIMS Medical Collage, Jaipur, Rajasthan, INDIA.
**Email:** jaindrkamalkumar@gmail.com

## Abstract

**Background:** Pulmonary arterial hypertension (PAH) is increasingly recognized disease in patients with renal disease. In a review, the prevalence of PHT in ESRD patients was reported to be around 40–50%. 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. Due to such increasing incidence of PH in CKD, present study was aimed to study pulmonary hypertension in various stages of chronic kidney disease at a tertiary care center. **Material and Methods:** Present cross-sectional and prospective study was conducted in Department of nephrology in patients with chronic kidney disease, diagnosed with pulmonary hypertension, willing for follow-up and participation in present study. **Results:** In present study, total 162 patients were included. Mean age in years was 45.19±13.26, while range of age was 19-76 years. Male patients (70%) outnumbered female patients. Co-morbidities in present study were anemia (78 %), systolic hypertension (28 %), diastolic hypertension ( 23%), diabetes mellitus ( 55%). Pulmonary hypertension was present in 66 (41 %) patients. In patients with pulmonary hypertension most common etiology for CKD were diabetes mellitus (41%), hypertension (32%), undetermined (6%), chronic tubulointerstitial disease (6%).In present study 28, 72 and 68 patients had CKD stage 3,4 and 5 respectively. Out of 66 patients with pulmonary hypertension 7, 23 and 36 patients had CKD stage 3,4 and 5 respectively. 45, 15 and 6 patients with pulmonary hypertension had mild (< 45 mph) ,moderate (45 - 60 mm hg) and severe (> 60 mm hg) pulmonary hypertension respectively. We compared few biochemical variables with pulmonary hypertension. P value was statistically significant in Hb <10 gm/dl and Ca × P product >55 mg2/dl2 patients. Total 90 patients were receiving hemodialysis in present study. Pulmonary hypertension was present in 43%,59% and 87% patients receiving hemodialysis for duration of < 6 months, 6 12 months and >12 months respectively. P value was statistically significant. **Conclusion:** In patients with CKD, presence of anemia, volume overload and increased calcium phosphate product can induce or aggravate pulmonary hypertension. In patients with hypertension and diabetes mellites, pulmonary hypertension is seen commonly.

**Key Words:** chronic kidney disease, haemodialysis, pulmonary hypertension, Calcium phosphate product

[*]**Address for Correspondence:**
Dr. Eshan Sharma, Associate Professor, Department of General Medicine, NIMS Medical Collage, Jaipur, Rajasthan, INDIA.
**Email:** jaindrkamalkumar@gmail.com
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## INTRODUCTION

Chronic kidney disease (CKD) includes a spectrum of pathophysiologic processes associated with abnormal kidney function and progressive decline in glomerular filtration rate (GFR). There are different stages of CKD which are stratified by both estimated GFR and the degree of albuminuria[1] .The prevalence and incidence of CKD are increasing worldwide[2]. Pulmonary arterial hypertension (PAH) is increasingly recognized disease in patients with renal disease. In a review, the prevalence of PHT in ESRD patients was reported to be around 40–

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50%[3]. Pulmonary hypertension, defined as systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiography, has been repeatedly reported in patients with chronic kidney disease, both predialysis and during regular renal replacement therapy, with a high but variable prevalence[4].End-stage renal disease commonly occurs with significant comorbidities, several of which may lead to PH. Left-side heart disease, chronic obstructive pulmonary disease, sleep apnea, collagen vascular diseases, HIV infection, and portal hypertension may coexist and result in PH. 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[5]. Elevated right atrial pressure leading to renal vein hypertension is increasingly recognized as a contributor to CKD. In turn, CKD may contribute to PH via increased renin-angiotensin-aldosterone-system activation and inflammatory response which have both been shown to be elevated in CKD and contribute to pulmonary vascular remodeling[6]. Due to such increasing incidence of PH in CKD, present study was aimed to study pulmonary hypertension in various stages of chronic kidney disease at a tertiary care center.

## MATERIAL AND METHODS

Present cross-sectional and prospective study was conducted in Department of nephrology, Department of General Medicine, NIMS Medical Collage, Jaipur. Study period was between September 2018 and September 2018. Institutional ethical committee approval was taken.

**Inclusion criteria**

Patients with chronic kidney disease, diagnosed with pulmonary hypertension, willing for follow-up and participation in present study

**Exclusion criteria included**

Smokers, any cardiovascular and pulmonary diseases (chronic obstructive lung disease, chest wall or parenchymal lung disease) which lead to pulmonary hypertension as well as patients with chronic coronary heart disease, previous pulmonary embolism, collagen vascular disease, volume overload at the time of echocardiography were excluded.

A written, informed consent was obtained for patients for participation. All patients included in this study underwent the following:

1. A detailed clinical examination including age; sex; smoking habits; associated comorbidity particularly diabetes mellitus and hypertension; age at time of CKD, etiology of renal failure, duration of dialysis treatment, and access location of AVF [brachial or radial].
2. Laboratory investigation included levels of hemoglobin, hematocrit, blood urea nitrogen, serum creatinine, serum bicarbonate, serum calcium, phosphorus, parathyroid hormone level. Average levels measured at least twice in the study period were calculated.
3. Transthoracic Doppler echocardiography: Every patient underwent a complete two-dimensional and Doppler echocardiography study on the day post dialysis within 4 h after completion of dialysis when the patient had reached the ‘‘dry weight’’ prescribed by nephrologists on the clinical examination including BP and weight in order to avoid overestimation of PAP due to volume overload. In PD patients there was no such specification.

All Transthoracic Doppler echocardiography examinations were done on (NAME OF EQUIPMENT) ultrasound machine. 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. All data was collected in a pre-designed proforma. Necessary statistical analysis was done.

## RESULTS

In present study, total 162patients were included. Mean age in years was 45.19±13.26, while range of age was 19-76 years. Male patients (70%) outnumbered female patients. Male: female ratio was 2.2:1. Co-morbidities in present study were anemia (78 %), systolic hypertension (28 %), diastolic hypertension ( 23%), diabetes mellitus ( 55%). In present study duration of CKD was 34.11+46.78 weeks, with 5-207 weeks range. Duration of dialysis was 12.45±15.74 weeks. 50 % patients had attained Dry weight in present study.

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**Table 1:** General characteristics of patients studied

| Variables Data | Mean±SD | No. of patients (%) |
|---|---|---|
| Age (years) | 45.19±13.26 | |
| Range | 19-76 | |
| Sex, | | |
| Male | | 114 ( 70%) |
| Female | | 52 ( 30%) |
| Co-morbidity | | |
| Anemia | | 126 (78 %) |
| Systolic Hypertension | | 46 (28 %) |
| Diastolic Hypertension | | 38 ( 23%) |
| Diabetes mellitus | | 89 ( 55%) |
| Duration of CKD (weeks) | 34.11+46.78 | |
| Range | 5-207 | |
| Duration of dialysis (weeks) | 12.45±15.74 | |
| Dry weight attained | | 81 (50%) |

**Table 2:** Pulmonary hypertension (PH) and etiology of CKD

| etiology of CKD | PH present | (%) | Total patients | P value |
|---|---|---|---|---|
| Diabetes Mellitus | 27 | 41% | 53 | <0.001 |
| Hypertension | 21 | 32% | 45 | <0.001 |
| Undetermined | 4 | 6% | 17 | 0.43 |
| Obstructive Uropathy | 1 | 2% | 9 | 0.08 |
| Chr.Glomerulonephritis | 2 | 3% | 9 | 0.16 |
| Chr.Tubulointerstitial disease | 4 | 6% | 9 | 0.10 |
| Polycystic Kidney disease | 2 | 3% | 8 | |
| Genitourinary TB | 1 | 2% | 4 | |
| Reflux disease | 1 | 2% | 2 | |
| Ischemic nephropathy | 2 | 3% | 5 | |
| Other (OTHER) | 1 | 2% | 1 | |
| **Total** | **66** | | **162** | |

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

| PH grades | Stage of CKD | | | Total |
|---|---|---|---|---|
| | 3 | 4 | 5 | |
| Absent | 21 | 49 | 26 | 96 |
| Mild < 45 mmHg | 6 | 17 | 22 | 45 |
| Moderate 45 - 60 mmHg | 1 | 4 | 10 | 15 |
| Severe > 60 mmHg | 0 | 2 | 4 | 6 |
| **Total** | **28** | **72** | **62** | **162** |

**Table 4:** Biochemical variables and pulmonary hypertension

| Variables | PH present (%) | PH absent (%) | Total | P |
|---|---|---|---|---|
| Hb <10 gm/dl | 110 (81%) | 26 (19%) | 136 | 0.001 |
| BUN >45 mg/dl | 53 (60%) | 35 (40%) | 88 | 0.19 |
| Sr. Creat >5 mg/dl | 78 (74%) | 28 (26%) | 106 | 0.03 |
| Ca × P product >55 mg2/dl2 | 16 (76%) | 5 (24%) | 21 | <0.001 |

**Table 5:** Duration of Hemodialysis (HD) and Pulmonary hypertension

| HD Duration (months) | PH present (%) | PH absent (%) | Total |
|---|---|---|---|
| < 6 | 9 (43%) | 12 (57%) | 21 |
| 6-12 | 23 (59%) | 16 (41%) | 39 |
| >12 | 26 (87%) | 4 (13%) | 30 |
| **TOTAL** | **58 (64%)** | **32 (36%)** | **90** |

p<0.001 (significant)

## DISCUSSION

The prevalence of chronic kidney disease (CKD) in the developed world is 13% and is recognized as a condition that elevates the risk of cardiovascular complications as well as kidney failure and other complications[7]. End-stage kidney disease (ESKD) substantially increases the risk of death, cardiovascular disease, and use of specialized health care. Pulmonary hypertension (PHT) has been reported to be high among end-stage renal disease (ESRD) patients. In clinical practice, shunting of blood from the left to the right side of the heart and increased cardiac output and pulmonary blood flow are common medical conditions resulting in PAH. Reported associations include arteriovenous fistulae, cardiac dysfunction, fluid overload, bone mineral disorder and non-biocompatible dialysis membranes[8]. Hormonal and metabolic derangement associated with end-stage renal disease might lead to pulmonary arterial vasoconstriction and an increase in pulmonary vascular resistance. 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. Pulmonary arterial pressure may be further increased by high cardiac output resulting from the arteriole-venous access itself, worsened by commonly occurring anemia and fluid overload[9]. Fibroblast growth factor 23 (FGF-23) is a marker of worsening renal function and has also recently been implicated as a causative factor in left heart disease. FGF-23 has also been shown to be elevated and predict prognosis in patients with CKD and pre-capillary PH[10,11]. The prevalence of PH in patients with ESRD ranges from 27% to 58%[12]. Patients with advanced CKD have a prevalence of PH that is lesser than that in patients with ESRD, ranging from 8% to 39%[13]. PH is an independent predictor of increased mortality in patients with CKD[13]. In present study we noted 41 % incidence of PH in patients with CKD. As per the data from the Indian Registry, the most common causes of CKD in India are diabetic nephropathy (30.3%) followed by chronic glomerulonephritis (15.8%) and hypertension (14.8%)[14]. Approximately 30% of patients with diabetes mellitus (DM) have diabetic nephropathy, and with the growing number of DM patients and aging population, there is likely a parallel increase in CKD incidence[15]. Hypertension and diabetes mellitus (DM) are dominant causes of kidney disease, trigger LV diastolic dysfunction, an alteration found to increase pulmonary venous and arterial pressure. Chronic volume overload, a factor implicated in LV disorders and in the high venous return in patients with CKD, may induce pulmonary venous hypertension by both increasing pulmonary blood flow and adversely affecting LV function. If sustained, vasoconstriction in the lung leads to extensive remodeling of the pulmonary vessels and a steady reduction in vessel compliance, a phenomenon which in and of itself contributes to pulmonary hypertension[16,17]. In present study most common etiology for CKD with pulmonary hypertension were diabetes mellitus (41%), hypertension (32%). PH was previously categorized as 'primary PH' or 'secondary PH' depending on whether it existed as an isolated disease or could be attributed to an identifiable predisposing condition. In 2003, however, an international consensus conference developed a new classification system for PH, which was modified in 2008. This framework was designed to be clinically relevant by grouping disorders with distinct pathophysiologies and distinct responses to treatment. Group 5 PH includes miscellaneous systemic diseases associated with PH with unclear or multifactorial mechanisms including sarcoidosis, myeloproliferative disorders, or glycogen- storage diseasesand patients with CKD or ESRD with 'unexplained PH'[18]. The standard test for confirmation of pulmonary hypertension is right heart catheterization[19], but the present study utilized echocardiography to screen patients of ESRD for presence of pulmonary hypertension because of its noninvasive nature, ease of application and repetition if required. Based on an echocardiographic diagnosis of PH, the reported prevalence of PH ranges from 9%–39% in individuals with Stage 5 Chronic Kidney Disease (CKD), from 18.8%–68.8% in hemodialysis patients, and from 0%–42% in patients on peritoneal dialysis therapy. Compared with the non-PH group, the patients with PH were significantly older, had lower eGFR, LVEF, hemoglobin, triglycerol, cholesterol, and LDL levels and increased incidences of diabetes, hypertension, mitral or aortal regurgitation, atrial fibrillation, pericardial effusion, cardiac dysfunction (systolic and diastolic) and previous CV events[20]. In present study incidence of PH was 41% in individuals with Stage 5 Chronic Kidney Disease (CKD) and 64% in hemodialysis patients. In a study by Agarwal *et al*, use of vitamin D activators was associated with lesser occurrence of PH[21]. Other associations found in various studies with development of PH in ESRD patients have been greater dialysis vintage, lower hemoglobin and smoking. However these associations were only seen in single studies[22, 23]. We also noted significant association between pulmonary hypertension with Hb <10 gm/dl and Ca × P product >55 mg2/dl. PH in ESRD is associated with increased mortality rates. Development of pulmonary hypertension has been found to be an independent predictor of increased mortality and poor outcome in patients

undergoing dialysis and renal transplant[24]. In an observational study, patients on haemodialysis with PH had mortality of 30.4% compared to 8.5% without PH[13]. During study period we noted 7% (11 patients) mortality.

## CONCLUSION

In patients with CKD, presence of anemia, volume overload and increased calcium phosphate product can induce or aggravate pulmonary hypertension. In patients with hypertension and diabetes mellites, pulmonary hypertension is seen commonly. Pulmonary hypertension is an independent predictor of mortality and morbidity in patients with CKD.

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