Original Research Article

Study of pulmonary arterial hypertension in patients of chronic kidney disease stage IV and V

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Abstract

Background: Pulmonary arterial hypertension (PAH) in advanced CKD patients (stage 4/5) is important to recognize, as PAH is an independent predictor of mortality in CKD patients especially those receiving renal replacement therapy and significant PH is felt to be a relative contraindication to renal transplantation. Present study was aimed to study Pulmonary Arterial Hypertension in Patients of Chronic Kidney Disease Stage 4/5 at a tertiary hospital. **Material and Methods:** Present study was cross-sectional, prospective and observational study, conducted patients Age ≥18 years, of either gender, diagnosed case of CKD in stage IV and stage V, underwent evaluation for PAH by echocardiography. **Results:** In present study, total 68 patients were included. Mean age in study was 51.93 ± 12.63 years. Male patients (73.53 %) outnumbered female patients (26.47 %). Associated Co-morbidities in present study were anemia (70.59 %), diabetes mellitus (57.35 %), systolic hypertension (32.35 %) and diastolic hypertension (26.47 %). majority of patients had stage 4 CKD (69.12 %). Mean duration of CKD was 43.11 + 26.78 weeks while mean duration of dialysis was 21.45± 15.74 weeks. 61.76 % patients had attained Dry weight in present study. In present study, incidence of pulmonary hypertension was 51.35 %. In patients with pulmonary hypertension most common etiology for CKD were diabetes mellitus (34.29%), hypertension (31.43 %), undetermined (17.14 %). In present study 47 patients (69.12 %) had stage 4 CKD. Among stage 4 patients mild PH was noted in 11 patients (16.18 %), while moderate and severe PH was noted in 4 (5.88 %) and 2 (2.94 %) patients respectively. While 21 patients (30.88 %) had stage 5 CKD. Among stage 5 patients mild PH was noted in 7 patients (10.19 %), while moderate and severe PH was noted in 5 (7.35 %) and 4 (5.88 %) patients respectively. **Conclusion:** Higher incidence of pulmonary hypertension is noted among chronic kidney disease and incidence increases with advanced stages.
Keywords: pulmonary hypertension, chronic kidney disease, dialysis, hypertension.

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INTRODUCTION

Chronic Kidney Disease (CKD) is defined as a condition with decreased kidney function shown by a Glomerular Filtration Rate (GFR) of less than 60 ml/minute per 1.73m2, or markers of kidney damage (abnormal urine sediments, renal imaging/ biopsy results) or both, of at least 3months duration, regardless of the underlying cause.[1,2] Diabetes and hypertension are responsible for nearly one third and one-fifth of CKD, respectively and obesity, smoking, aging are also causes of CKD.[3] CKD is associated with increased incidences of cardiovascular mortality and loss of disability adjusted quality of life (QOL) years.[4] Pulmonary hypertension (PH) comprises a

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group of clinical and pathophysiological entities due a variety of underlying causes related to heart, lung or systemic disorders. Regardless of the etiology, morbidity and mortality from long-standing PHT exceed that expected from the causative condition.[1] 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] PH in advanced CKD patients (stage 4/5) is important to recognize, as PH is an independent predictor of mortality in CKD patients especially those receiving renal replacement therapy and significant PH is felt to be a relative contraindication to renal transplantation.[6] Present study was aimed to study Pulmonary Arterial Hypertension in Patients of Chronic Kidney Disease Stage 4/5 at a tertiary hospital.

MATERIAL AND METHODS

Present study was cross-sectional, prospective and observational study, conducted in Department of General Medicine, Sri Siddhartha Institute Of Medical Sciences And Research Centre, T. Begur. Study period was of 2 years (from September 2019 and August 2020). Study approval was taken from institutional ethical committee.

Inclusion criteria: Patients Age ≥18 years, of either gender, diagnosed case of CKD in stage IV and stage V.

Exclusion criteria: Valvular heart disease, congenital heart diseases**.** Chronic obstructive pulmonary disease, Chronic parenchymal lung disease**.** Chronic liver disease, Connective tissue diseases, Hypothyroidism and hyperthyroidism, Chronic thromboembolic disorders**.** Pregnancy**.** Chronic smokers**.** Patients not willing to participate.

Study was explained and a written; informed consent was obtained from patients for participation.

Patients details such as demographic data, past history (age; sex; smoking habits; associated comorbidity particularly diabetes mellitus and hypertension; age at time of CKD, etiology of renal failure, duration of dialysis treatment) were collected. Patients underwent detailed clinical examination and findings were recorded in CRF. Laboratory investigation included levels of hemoglobin, hematocrit, blood urea nitrogen, serum creatinine, serum bicarbonate, serum calcium, phosphorus, parathyroid hormone level. All patients underwent a transthoracic 2D 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.

PAH 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)

All data was collected in a pre-designed proforma. Necessary statistical analysis was done.

RESULTS

In present study, total 68 patients were included. Mean age in study was 51.93 ± 12.63 years. Male patients (73.53 %) outnumbered female patients (26.47 %). Associated Co-morbidities in present study were anemia (70.59 %), diabetes mellitus (57.35 %), systolic hypertension (32.35 %) and diastolic hypertension (26.47 %). majority of patients had stage 4 CKD (69.12 %). Mean duration of CKD was 43.11 + 26.78 weeks while mean duration of dialysis was 21.45± 15.74 weeks. 61.76 % patients had attained Dry weight in present study.

Table 1: General characteristics of patients studied

Variables Data	No. of patients / Mean ± SD	Percentage (%)
Age (years)	51.93 ± 12.63	
Gender		
Male	50	73.53
Female	18	26.47
Co-morbidity		0.00
Anemia	48	70.59
Systolic Hypertension	22	32.35
Diastolic Hypertension	18	26.47
Diabetes mellitus	39	57.35
Stage of CKD		0.00
Stage 4	47	69.12
Stage 5	21	30.88
Duration of CKD (weeks)	43.11 + 26.78	
Duration of dialysis (weeks)	21.45± 15.74	
Dry weight attained	42	61.76

In present study, incidence of pulmonary hypertension was 51.35 %. In patients with pulmonary hypertension most common etiology for CKD were diabetes mellitus (34.29%), hypertension (31.43 %), undetermined (17.14 %).

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

Etiology of CKD	No. of patients (n=68)	Percentage (%)	No. of patients with pulmonary hypertension (n=68)	Percentage (%)
Diabetes Mellitus	25	36.76	12	34.29
Hypertension	19	27.94	11	31.43
Undetermined	10	14.71	6	17.14
Obstructive Uropathy	4	5.88	2	5.71
Ch. Glomerulonephritis	3	4.41	1	2.86
Ch. Tubulointerstitial disease	3	4.41	1	2.86
Polycystic Kidney disease	2	2.94	1	2.86
Genitourinary TB	1	1.47	0	0.00
Ischemic nephropathy	1	1.47	1	2.86

In present study 47 patients (69.12 %) had stage 4 CKD. Among stage 4 patients mild PH was noted in 11 patients (16.18 %), while moderate and severe PH was noted in 4 (5.88 %) and 2 (2.94 %) patients respectively. While 21 patients (30.88 %) had stage 5 CKD. Among stage 5 patients mild PH was noted in 7 patients (10.19 %), while moderate and severe PH was noted in 5 (7.35 %) and 4 (5.88 %) patients respectively.

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

Pulmonary hypertension grade	Stage of CKD (n=68)		Total
	Stage 4	Stage 5	
Absent	30 (44.12 %)	5 (7.35 %)	35 (51.47 %)
Mild < 40 mmHg	11 (16.18 %)	7 (10.29 %)	18 (26.47 %)
Moderate 40 - 60 mmHg	4 (5.88 %)	5 (7.35 %)	9 (13.24 %)
Severe > 60 mmHg	2 (2.94 %)	4 (5.88 %)	6 (8.82 %)
Total	**47 (69.12 %)**	**21 (30.88 %)**	**68**

DISCUSSION

In common clinical practice, PAP is estimated by echocardiography using the modified Bernoulli equation:[7] PAP=4 X (tricuspid systolic jet velocity)^2 + estimated right atrial pressure, typically measured by vena cava diameter or added based on an assumed, fixed value. Prevalence of PH increased with CKD severity, from 21% in CKD G3a to 32.8% in CKD G5. Older age, anemia, reduced left ventricular ejection fraction (LVEF), and LV hypertrophy were associated with greater risk of PH on adjusted analysis; eGFR was not independently associated with PH risk.[8] In study by Mehta K *et al.*,[9] among 200 CKD patients, prevalence of PH in CKD patients was 60.5%, with mean pulmonary artery systolic pressure (PASP) of 38.52 ± 7.32 mmHg. The mean age of those with PH was 47.85 ± 13.09 years. PH was more common in males ($p = 0.03$). The prevalence of PH increased as CKD stage advanced ($p < 0.001$). Diabetes and hypertension had a strong association with PH ($p < 0.001$). The prevalence ($p = 0.003$) and severity ($p = 0.011$) of PH increased with increase in CKD duration. In patients on hemodialysis (HD), the prevalence ($p < 0.001$) and severity ($p = 0.022$) of PH was significant compared to those on conservative treatment. The prevalence ($p < 0.001$) and severity ($p < 0.001$) of PH significantly increased as duration of HD increased. Serum creatinine ($p = 0.02$) and serum calcium-phosphorus product ($p < 0.001$) were significantly higher in patients with PH. In study by Mann A *et al.*,[10] out of 100 CKD patients, Pulmonary arterial hypertension (PAH) was found in 61 patients, of which 23 had mild, 34 had moderate and 4 had severe PAH. Significant association was seen of systolic and diastolic blood pressure with high systolic blood pressure also associated with increased PAH severity. Significant association was seen of haemodialysis, arteriovenous fistula (AVF), CKD severity and haemodialysis duration. Increased hemodialysis duration and AVF were significantly associated with PAH severity also. Anaemia, low calcium, high phosphate, increased calcium phosphate product and increased intact-parathormone were significantly associated with PAH while except calcium, these were also significantly associated with increased PAH severity. Jared M. *et al.*,[11] studied 4635 patients who underwent catheterization: 1873 (40%) had CKD; 1518 (33%) stage 3, 230 (5%) stage 4, and 125 (3%) stage 5. Pulmonary Arterial Hypertension (PH) was present in 1267 (68%) of these patients. Post-capillary (n=965, 76%) was the predominant PH phenotype among CKD patients versus 302 (24%) for pre-capillary ($P<0.001$). CKD was independently associated with pulmonary hypertension (odds ratio 1.4, 95% confidence interval¼1.18–1.65). Mortality among CKD patients rose with worsening stage and was significantly

increased by PH status. Zhang *et al.* [12], noted that the prevalence of PH increased with increased CKD stage, however, which had no direct relation to the severity of PH. They found that moderate to severe PH might occur in any stages of CKD, indicating that PH was a multi-factorial disorder in ESRD. They also explained that this result might be due to the prostacyclin therapy used for the treatment of CKD stage 3-5, which has a cytoprotective and antiproliferative effect and hence, the distribution of mild-moderate severe PH in CKD stage 3–5 might be varied due to prostacyclin. Among 108 patients of CKD, Suresh H *et al.*, [13] noted that mean age of studied population was 43.53 ± 14.63 years. Sex ratio was 2.72:1 (male: female). PH was present in 47 of 108 (43.5%) cases at beginning, 41 of 83 (491.4%) at 3 months, and 32 of 64 (50%) at 6 months. The prevalence and severity of PH increased with progression of CKD stage, although not statistically significant. Heart failure with reduced ejection fraction and heart failure with preserved EF were significantly higher among PH group compared to non-PH group ($P < 0.01$). Control of fluid overload, the use of beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and optimization of dialysis appear to be the most important methods to treat HF in CKD and ESRD patients. Aldosterone antagonists and digitalis glycosides may additionally be considered; however, their use is associated with significant risks. [14] Importantly, early detection and treatment of diabetes, hypertension, and CKD is possible using readily available, often inexpensive, treatments. These interventions can improve renal and cardiovascular outcomes and slow or prevent progression to ESKD.[15,16]

CONCLUSION

Higher incidence of pulmonary hypertension is noted among chronic kidney disease and incidence increases with advanced stages. Thus early evaluation of CKD patients for hemodynamic changes leading to pulmonary hypertension and also for other causes of PAH by echocardiography is strongly recommended.

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