Section A-Research paper

STUDY OF PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC KIDNEY DISEASE IN A TEACHING HOSPITAL

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ABSTRACT

Background: Pulmonary hypertension is defined as a mean artery pressure ≥25 mm Hg and is a serious and progressive complication of chronic kidney disease and end-stage renal disease. Identifying pulmonary arterial hypertension (PAH) can be challenging but is important in this population since management strategizes differ from those for patients with ESKD who donot have PH.

Aim of the study : To study the occurrence of PAH in CKD stage 4 and 5 and to study the risk factors for development of PAH in these patients.

Material & Method: This was an observational cross section study conducted on 85 patients of CKD stage 4 and 5 (based on KDIGO 2012 criteria) admitted to the medicine wards in Mamata academy of medical sciences, bachupally Hyderabad from the year 2022-2023

Result: In our study 35.2 % cases showed no PAH .Mild PAH noted in 23.5% cases , Moderate PAH noted in 36.4% cases and 4.7% showed severe PAH . systolic and diastolic blood pressure with PH showed significant association .Presence of haemodialysis significantly associated with PH. Significant association was seen with age and BMI. Low haemoglobin was also significantly associated with PH. Low serum calcium, high serum phosphate, increased calcium phosphate product were also significantly associated with presence of PH. Patients with PH had lower LVEF% showed a statistical significant correlation with p value less than 0.0001.

Conclusion: CKD patients have a higher prevalence of pulmonary hypertension. The prevalence of pulmonary hypertension is high in stage 5 CKD patients, and it is also higher in dialysis patients.

Key words : CKD,PAH, Low haemoglobin.

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 agroup of clinical and pathophysiological entities due a variety of underlying causes related to heart, lung or systemic disorders.[4]

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (PAP) >25 mm Hg as measured by right heart catheterization. PH may be secondary to an underlying cardiac or pulmonary process or may result de novo when an intrinsic pulmonary arteriopathy occurs. Regardless of the mechanism, prolonged elevation in PAP leads to right ventricular dysfunction and consequent morbidity and mortality.[5,6,7.]PH has recently been recognized as a common complication of chronic kidney disease (CKD) and end-stage renal disease (ESRD)

The pathogenesis of PAH is not fully elucidated in patients of CKD [8]. It is considered to be because of the interaction of multiple aspects of altered cardiovascular physiology, elevated left ventricular filling pressure and pulmonary venous hypertension due to myocardial dysfunction are some of the important causes of PAH in CKD. The other important factors implicated are increased cardiac output (CO),[9] volume overload, anemia, increased pulmonary blood flow due to shunting across arteriovenous fistula (AVF),[10,11] endothelial dysfunction leading to pulmonary vasoconstriction,[10] decreased compliance of pulmonary vasculature, exposure to dialysis membranes, pulmonary artery calcification and stiffening secondary to hyperparathyroidism, increased thromboxane B2 , and increased brain natriuretic peptide.[11]

The symptoms and signs of PH in patients with ESKD are the same as in those ESKD (eg Progressive dyspnea ,fatigue ,syncope ,signs of right heart failure) .Similar to PH associated with other etiologies ,PH in patients with ESKD is progressive and may be suspected when PH progresses in severity and right hear failure develops.

PAH is an independent predictor of increased mortality in patients with CKD and its presence has been recently suggested to be associated with a poor outcome [12] in these patients. Hence further studies are needed to assess the association of PAH in CKD patients. This study was conducted to study the occurrence of PAH in CKD focusing on stage IV and V patients and to study the risk factors for development of PAH in CKD stage IV and V.

MATERIALS AND METHODS

This was an observational cross section study conducted on 85 patients of CKD stage 4 and 5 (based on KDIGO 2012 criteria) attending medicine OPD at Mamata academy of medical sciences Bachupally Hyderabad from 2022-2023.

Each patient was subjected to detailed history and clinical examination and relevant investigations were done including CBC,RFT, random blood sugar, S. Calcium, S. Phosphate, S. uric acid, routine urine examination and microscopy, USG abdomen, Chest X-Ray, ECG and 2Dechocardiography.

PAH was diagnosed on the basis of echocardiography with mean pulmonary arterial pressure (MPAP) of ≥25mmHg.

. Pulmonary hypertension was classified as:

Mild (25-40 mmHg)

Moderate (40-60 mmHg)

Severe (>60 mmHg)

Inclusion Criteria

- Patients of CKD in stage IV and stage V.
- Age 40 to more than 70 years.

Exclusion Criteria

- Age less than 40 years
- Valvular heart disease
- Congenital heart diseases
- Chronic obstructive pulmonary disease
- HIV-infected patients
- Chronic liver disease
- Hypothyroidism , Hyperthyroidism.
- Pregnancy
- Lactation

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median.

1. Quantitative variables were compared using Unpaired t-test/MannWhitney Test (when the data sets were not normally distributed) between CKD Stage 4 and 5.
2. . Qualitative variables were compared using Chi-Square test / Fisher's exact test. A p value of < 0.005 was considered as significant .

RESULTS

In the present study age distribution ranged from 40 years to more than 70 years .Majority were noted among 51-60 years constituting 82.3% cases.11.7% constituted among 40-50 years and 5.8% in more than 70 years .Mean age is 55.95± 5.63.Males were predominant and constituted 58.8% when compared to females (41.5%).

Table 1 : Distribution of 2D echo findings

2D echo findings	No. of cases	Percentage
Ejection fraction < 35% >35%	 55 30	 64.7 35.2
PAH • Mild • Moderate • Severe	 20 31 4	 23.5 36.4 4.7
Left ventricular hypertrophy	10	11.7
Ischemia	20	23.5
Pericardial effusion	02	2.3
Diastolic dysfunction	10	11.7
Systolic dysfunction	12	14.1

In our study 35.2 % cases showed no PAH .Mild PAH noted in 23.5% cases , Moderate PAH noted in 36.4% cases and 4.7% showed severe PAH . LV Diastolic Dysfunction was significantly present in 10 (11.7%) , Mild Pericardial effusion was seen in 2 (2.3%) patients.

Left ventricular systolic dysfunction was present in 12 (14.1%). ischemia seen in 20(23.5%) cases.
CKD stage 4 seen in 50.5% cases (43/85) and 49.4% (42/85) cases were having CKD stage 5 .CKD stage 4 was seen in 11.7% (10/85) cases of Mild PAH , 18.8% (16/85) and 2.3% (2/85) of moderate and severe PAH .CKD stage 5 was seen in 11.7% (10/85) cases of Mild PAH , 17.6% (15/85) and 2.3% (2/85) of moderate and severe PAH .

BMI of 18.5 to 25 seen in 10.5% (9/85) , 9.4% (08/85) and 1.1% (01/85) in mild ,moderate and severe PAH cases .BMI of 26-29 seen in 11.7% (10/85) , 24.7% (21/85) and 3.5% (03/85) in mild ,moderate and severe PAH cases .BMI of 18.5 to 25 seen in 10.5% (9/85) , 9.4% (08/85) and 1.1% (01/85) in mild ,moderate and severe PAH cases respectively .

SBP of 140-159 mm Hg seen in 9.4% (8/85) , 10.5% (09/85) and 1.17% (01/85) in mild ,moderate and severe PAH cases SBP of more than 160 mm Hg seen in 14.1% (12/85) , 25.8% (22/85) and 3.5% (03/85) in mild ,moderate and severe PAH cases .

DBP of 80-89 mm Hg seen in 10.5 % (9/85) in severe PAH cases , 90-99 mm Hg seen in 11.7% (10/85) , 24.7 (21/85) and 1.17% (01/85) in mild ,moderate and severe PAH cases . 90-99 mm Hg seen in 11.7% (10/85) , 24.7 (21/85) and 1.17% (01/85) in mild ,moderate and severe PAH cases . >100 mm Hg seen in 11.17%(1/85),14.1% (12/85) and 3.5%(3/85) in mild, moderate and severe PAH cases ,

Haemodialysis was done in 9.4% (8/85) , 17.6%(15/85) and 2.3% (2/85) in mild ,moderate and severe PAH cases.

Diabetes seen in in 11.7% (10/85) , 20%(17/85) and 1.17% (1/85) in mild ,moderate and severe PAH cases.

Mild anaemia seen in 7.05% (6/85) , 17.6%(15/85) and 1.17% (1/85) in mild ,moderate and severe PAH cases. Moderate anaemia seen in 5.8% (5/85) , 7.0%(15/85) and 1.17% (1/85) in

mild ,moderate and severe PAH cases. Severe anaemia seen in 10.5% (9/85) , 11.7%(10/85) and 2.3% (2/85) in mild ,moderate and severe PAH cases.

Serum uric acid of 3.5 to 7.2 mg/dl seen in 17.6% (15/85) , 23.5%(20/85) and 2.3% (2/85) in mild ,moderate and severe PAH cases. Serum uric acid of >7.2 mg /dl seen in 5.8% (5/85) , 12.9%(11/85) and 2.3% (2/85) in mild ,moderate and severe PAH cases.

Serum uric acid of <8.5 mg/dl seen in 17.6% (15/85) , 23.5%(20/85) and 2.3% (2/85) in mild ,moderate and severe PAH cases. Serum uric acid of >7.2 mg /dl seen in 5.8% (5/85) , 12.9%(11/85) and 2.3% (2/85) in mild ,moderate and severe PAH cases.

Serum Phosphate of 3.4 to 4.5 mg/dl seen in 7.6% (6/85) ,12.9%(11/85) and 1.17% (1/85) in mild ,moderate and severe PAH cases. And >6 mg /dl seen in16.5% (14/85) , 23.5%(20/85) and 3.5% (2385) in mild ,moderate and severe PAH case.

Calcium Phosphate Product of <55 mg^2/dL^2 seen in 2.3% (1/85) , 1.17%(1/85) and 1.17% (1/85) in mild ,moderate and severe PAH cases. Calcium Phosphate Product of <55 mg^2/dL^2 seen in 21.1% (18/85) , 35.2%(30/85) and 3.5% (3/85) in mild ,moderate and severe PAH cases.

Anaemia, low calcium, high phosphate, increased calcium phosphate product and increased intact-parathormone were significantly associated with PAH.

Table 3: Characteristics of patients with and without PAH

Parameters	Without PAH(n=30)	With PAH (n=55)	P value (Exact)[a]
	Mean ± SD		
Age	53.34 ± 4.099	57.30 ± 5.874	0.0026 **
BMI	24.14 ± 0.8752	28.29 ± 3.874	<0.0001 ****
SBP	119.7± 4.211	168.8 ± 14.62	<0.0001 ****
DBP	80.00 ± 0.000	95.27 ± 5.210	<0.0001 ****
HB	12.96 ± 0.8065	8.591 ± 1.442	<0.0001 ****
Serum Calcium	9.412 ± 0.3475	7.512 ± 1.755	<0.0001 ****
Serum Uric Acid	5.541 ± 0.6538	7.196 ± 2.663	0.0995 ns
Serum Phosphate	4.886 ± 0.6474	7.854 ± 2.072	<0.0001 ****
calcium phosphate prod	44.69 ± 5.989	61.73 ± 8.400	<0.0001 ****

Ejection Fraction	52.14 ± 3.056	34.50 ± 4.234	<0.0001 ****

[a] *Mann-Whitney unpaired t test, P<0.05, *= significant. ns= not significant*

Significant association was seen of systolic and diastolic blood pressure with PH. Presence of haemodialysis significantly associated with PH. Significant association was seen with age and BMI. Low haemoglobin was also significantly associated with PH. Low serum calcium, high serum phosphate, increased calcium phosphate product were also significantly associated with presence of PH. Patients with PH had lower LVEF% showed a statistical significant correlation with p value less than 0.0001.

No significant association was seen with S. Uric acid with presence of PH.

Table 4 : Characteristics of patients with and without PH

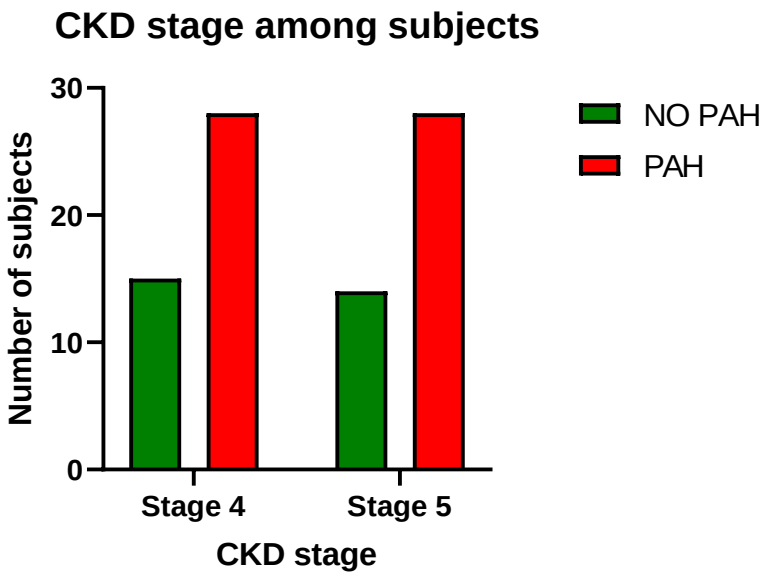
Parameters	Without PAH (n=30)	With PAH (n=55)	P value (Exact)[a]
CKD stage 4	15	28	>0.9999 ns
CKD stage 5	14	28	>0.9999 ns
Presence of Hemodialysis	0	24	<0.0001 ****
2D Echo Findings			
Presence of Ischemia	0	20	<0.0001 ****
Presence of Pericardial Effusion	0	2	0.5451 ns
Presence of SD	0	12	0.0066 **
Presence of DD	0	10	0.0137 *

*Fischer's exact test, P<0.05, *= significant. ns= not significant*

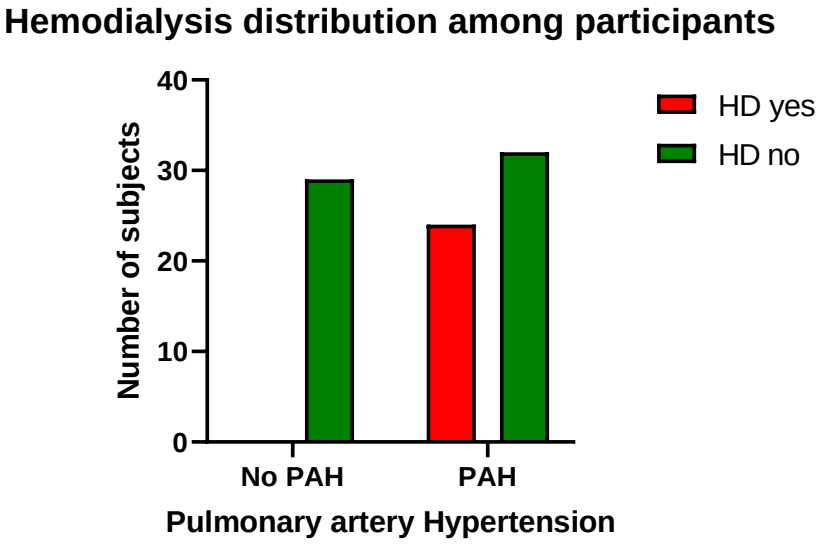
Characteristics of patients with and without PH Presence of Hemodialysis shows a statistical significant correlation with p value less than 0.0001.
Among 2D echo findings presence of Ischemia shows a statistical significant correlation with p value less than 0.0001.

On performing univariate logistic regression analysis, increased systolic blood pressure, increased diastolic blood pressure, , low hemoglobin, low serum calcium, increased serum phosphate, increased calcium phosphate product, low LVEF, higher CKD stage and hemodialysis were found to be significant risk factors of pulmonary hypertension.

In our study we did not found a significant association between stage of CKD and severity of PH.



Graph 1 : CKD stage among subjects



Graph 2 : Distribution of hemodialysis among participants

Table 5 : Characteristics of patients with ,ild ,moderate and severe PAH

Parameters	Mild PH (n=20)	Moderate PH (n=31)	Severe PH (n=4)	P value [a]
	Mean ± SD			

Age	54.25 ± 2.789	57.63 ± 5.008	70.00 ± 6.782	0.0002 ***
BMI	26.10 ± 2.269	29.34 ± 4.240	30.75 ± 2.217	0.0052 **
SBP	163.8 ± 13.19	170.6 ± 15.24	179.5 ± 7.767	0.0685 ns
DBP	91.60 ± 6.369	96.72 ± 2.453	102.0 ± 2.449	0.0005 ***
HB	8.345 ± 1.347	8.841 ± 1.449	7.825 ± 1.756	0.4668 ns
Serum Calcium	7.140 ± 1.586	7.724 ± 1.827	7.675 ± 2.142	0.6347 ns
Serum Uric Acid	6.475 ± 2.342	7.484 ± 2.764	8.500 ± 3.121	0.1925 ns
Serum Phosphate	8.150 ± 2.008	7.428 ± 2.093	9.775 ± 0.66	0.0373 *
calcium phosphate prod	62.25 ± 9.503	62.25 ± 7.833	55.00 ± 4.761	0.2520 ns
Ejection Fraction	39.10 ± 0.9679	31.50 ± 2.851	35.50 ± 0.577	<0.0001****

[a] *One way ANOVA(Kruskal-Wallis test), P<0.05, *= significant. ns= not significant*

Age ,BMI ,DBP and Ejection Fraction showed a significant correlation with the severity of PH.

DISCUSSION

Pulmonary arterial Hypertension (PH) and Chronic Kidney Disease (CKD) both profoundly impact patient outcomes, whether as primary disease states or as co-morbid conditions. PH is a common co-morbidity in CKD and vice versa. In our study the prevalence of PH in CKD patients in the present study was **64.7%. Kalpana et al**[13] noted the prevalence of PH in CKD patients as 60.5% .**Meroz et al**[14] noted Prevalence of PH in CKD 44%

In the present study CKD stage 4 was seen in 11.7% cases of Mild PAH , 18.8% and 2.3% of moderate and severe PAH .CKD stage 5 was seen in 11.7% cases of Mild PAH , 17.6% and 2.3% of moderate and severe PAH .In **Sohan et al study**[15] 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. . **In Atul mann study** [16] 50% patients were of CKD stage 4 and 50% patients were of CKD stage 5. PH was noted in 38% patients in CKD stage 4 and 84% patients in CKD stage 5 inferring that more advanced the CKD stage is, the higher is the incidence of PH.

In the present study age distribution ranged from 40 years to more than 70 years .
Majority were noted among 51-60 years constituting 82.3% cases.11.7% constituted among 40-50 years and 5.8% in more than 70 years .Mean age is 55.95± 5.63. Males were more constituting 58.8% when compared to females (41.5%) . These results were consistent with other studies.[17,18,19].

We found a ssignificant association on prevalence of PH with age and BMI **,** where as in **Atul mann et al [16]**study there was no effect of age and sex of the patients on prevalence of PH . However, in contrast, **Zhang et al[20]** found that BMI was a significant risk factor of PH. **Vinayak et al study [21]**the mean age of the patients was found to be 49.45±8.97yrs, with majority of the patients in age group of 41-60yrs. On gender assessment majority of the patients were male (68%), with male preponderance. There is no significant difference in mean age of the patients with pulmonary hypertension and patients without PHT. Similarly, there is significant higher incidence of age group among the patients with PHT. ($p<0.05$).**Kalpana et al** [13]PH was more common in males than females and statistically significant ($p = 0.03$). There was statistically significant association between CKD stages and PH ($p < 0.001$). **Sohan et al** [15]mean age in study was 51.93 ± 12.63 years. Male patients (73.53 %) outnumbered female patients (26.47 %).

In our study there was a statistically significant association between raised SBP and DBP with PH .Similar findings were observed in **Atul mann** study[16] ,**Navaneethan et al[22]** stduy ,but a study conducted by **H. Suresh et al [23]** and **Y. Havluku et al [24]** did not find the association of SBP, DBP with PH to be significant.

In our study, significant association was seen in diastolic blood pressure with severity of PH .In **Atul mann et al study[15]** significant association was seen in systolic blood pressure with severity of PH while no significant association was seen in diastolic blood pressure with stage of PH while no significant association was seen in systolic blood pressure with stage of PH. In studies by **Zhang et al [20] and K. Ramasubbu et al [25]** no significant association was seen in either systolic blood pressure or diastolic blood pressure with severity of PH.

In our study we did not found a significant association between stages of CKD and severity of PH. Where as **Atul mann et** al[16]and **H. Suresh et al[23]** found a significant association between CKD and severity of PAH.

In our study diabetes seen in in 11.7% , 20%and 1.17% in mild ,moderate and severe PAH cases. There was a statistical significance between diabetes and hypertension with PH ($p < 0.001$) .In **Kalpana et al** [13] study 54 diabetics (85.71%) had PH whereas 30 out of 52 hypertensives (57.69%) had PH. There was a strong association between diabetes and hypertension with PH ($p < 0.001$) .

In our study a significant increase in BMI (kg/m^2) with severity of pulmonary hypertension was seen. Similar results were observed by **Zhang et al[20] And Atul mann et al** [16] where patients with higher BMI had severe PH.

In the Present study low haemoglobin, increased serum phosphate, increased calcium phosphate , increased calcium phosphate product, low LVEF and hemodialysis were found to be significant risk factors of pulmonary hypertension. Similar findings were observed in **Atul mann et al study[16] .In Sohan et al study [15]** associated Co-morbidities were anaemia (70.59 %), diabetes mellitus (57.35 %), systolic hypertension (32.35 %) and diastolic hypertension (26.47 %). majority of patients had stage 4 CKD (69.12 %).

Our study showed no significant association of increased phosphate, increased calcium phosphate product with the severity of PH. Similar findings were observed in **Zhang et al [20]study ,**In contrast **atul mann et al** [16]showed a significant association of increased phosphate, increased calcium phosphate product with the severity of PH.

Limitations of our Study

Our study was an observational study with stages 4 and 5 cases of CKD, we did not included CKD stage 1 to 3. A follow up will give a better assessment of severity of PAH and mortality . PAH was diagnosed by Echocardiography which is observer dependent.

CONCLUSION

In our study the prevalence of pulmonary hypertension is high in stage 5 CKD patients, and it is also in dialysis patients. In CKD patients, there is no gender difference in the development of pulmonary hypertension. Decreased haemoglobin in, lower serum calcium, and a high phosphorus value are all associated with pulmonary hypertension in CKD patients.

Patients with ESKD and PH should exercise as tolerated ,Receive routine vaccinations ,be counselled against smoking and vaping and maintain a normal body mass index when indicated .they should also be treated with oxygen and diuretics (when feasible)

We typically manage volume aggressively .We optimize therapies for any co morbidities known to be associated with or worsen PH ,particularly heart failure ,obstructive sleep apnoea and underlying lung disease .

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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