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Original Research Article

Study of pulmonary hypertension in chronic kidney disease and correlation of pulmonary hypertension with staging of chronic kidney diseases in tertiary care center in central India

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Abstract

Background: Pulmonary hypertension (PH) has been recently reported to be a common co-morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD). The present study was conducted to analyze the prevalence of PH in patients with CKD, its severity in different stages of CKD, and risk factors for it. **Method:** A total171 patients of age >18 years, diagnosed with CKD were included in the study and were classified in various stages of CKD (1-5) according to eGFR. eGFR was calculated by the MDRD formula (KDIGO-2010).**Result:** Among total CKD patients, 53.22% were in stage V, 26.9% in stage IV and 19.88% in Stage III. Low hemoglobin, high phosphorus, high Ca-po4 product, and high serum creatinine were significantly associated with higher stages of CKD, ($P<0.05$).Prevalence of PH in CKD patients was 39.18%. Among these 59 had mild PH, 8 had moderate PH.Maximum patients with PH were having etiology of combined diabetes mellitus with hypertension, ($P<0.05$). Patients of CKD having duration of >5 years, patients on hemodialysis and patients with AV fistula had a greater number of PH with significant p value, ($P<0.05$). The relation of PH according to stage of CKD showed that Stage V had greater PH compared to Stage III, ($P<0.05$).Patients with Stage V had more patients with moderate PH compared to patients with Stage III, ($P<0.05$)**Conclusion:** PH is more prevalent in patients with CKD. The severity of PH directly correlates with Stages of CKD i.e., an increase in severity of PAH occurs with deterioration of renal function in CKD cases.

Keywords: Pulmonary hypertension (PH), chronic kidney disease (CKD), End-stage renal disease, MDRD formula; eGFR; Hemodialysis

Introduction

Chronic kidney disease (CKD)is a worldwide public health problem with a global estimated prevalence of CKD being 13.4% (11.7-15.1%). Also, patients with end-stage kidney disease (ESKD) needing renal replacement therapy are estimated between 4.902 and 7.083 million [1]. The approximate prevalence of CKD is 800 per million population with the incidence of ESRD being 150–200 per million population [2].CKD are more likely to die of CVD than to reach ESRD, so severity may have been underestimated [1].

Pulmonary hypertension (PH), defined as systolic pulmonary artery pressure (SPAP) > 35 mmHg at rest as estimated by Doppler echocardiography, has been repeatedly reported in patients with CKD [3].Among patients with essential hypertension, approximately 6% have CKD, also they are at increased risk for progression to ESRD. PH might be induced and/or aggravated by left ventricular disorders, volume overload, AVF, sleep-disordered breathing, exposure to dialysis membranes, endothelial dysfunction, vascular calcification and stiffening, and severe anemia. However, PH is highly prevalent in adults with CKD and is associated with increased mortality rates in ESRD patients. In the classification of PH, PH in CKD is placed in a diverse group with unclear or 3 multifactorial mechanisms (Class 5), although the underlying cardiovascular disease may account for the majority of cases [4].

Despite the higher prevalence of PH in CKD and kidney failure as shown by several studies, along with an association with poor outcomes, not much evidence is available for its diagnostic and management strategies in those with CKD. In CKD patients not yet requiring kidney replacement therapy, volume management along with management of underlying risk factors of PH is critical. For patients on hemodialysis, management options are limited, and they may require transition to peritoneal dialysis if recurrent hypotension precludes optimal volume control [5].Despite having a prognostic significance, the actual prevalence of PH in CKD is unclear. Also, not much data is available on the incidence and prevalence of PH in CKD among Indian patients. Here, we focus on the prevalence of PH and CKD staging. Therefore, present study was conducted in a tertiary care institute in the central India region to see the prevalence of PH and any relationship between the severity of PH in patients with clinical staging of CKD.

Material and Methods

After obtaining Institutional Ethical Committee approval and written informed consent from all the patients, this observational cross-sectional study was conducted at the outpatient department (OPD) of the Tertiary Care Hospital in an urban setup during a period from October 2019 to September 2021. A total of 171 patients diagnosed with CKD of aged group >18 years was included in the study. All known cases of PH secondary to left-sided heart diseases (e.g., coronary heart diseases with normal LV function, rheumatic heart diseases, and valvular heart diseases), patients with other systemic disorders that can cause PHs (such as collagen vascular diseases; SLE, Scleroderma, HIV infection, Hyperthyroidism and Hypothyroidism, and Chronic liver disease), patients with pulmonary diseases (Bronchial Asthma, COPD, pulmonary embolism, and scleroderma) and pregnant women were excluded from the study.

Chronic Kidney Disease (CKD): Gradual decline in GFR more than or equal to 3 months duration.

Table 1: CKD classification based on Glomerular filtration rate: [6]

Stage	GFR, mL/min per 1.73 m^2
1	>90
2	60–89
3	30-59
4	15–29
5	<15

Pulmonary Hypertension [7]:

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. PH was further categorized as mild (35-49 mmHg), moderate (50-69 mmHg), and severe (≥70mmHg).

All patients underwent detailed clinical evaluation. Medical history including age, sex, associated comorbidity, particularly diabetes and hypertension, symptoms of CKD, CKD etiology and duration, dialysis and its duration, and presence or absence of AV Fistula, presence or absence of symptoms congestive heart failure was taken.Laboratory investigations like complete blood count, urine protein by dipstick, blood urea nitrogen (BUN), serum creatinine, serum sodium and potassium, serum calcium, and phosphate were done by standard laboratory

methods. eGFR was calculated by the MDRD formula (KDIGO-2010). All patients were classified in various stages of CKD (1-5) according to eGFR. Chest X-ray was done to exclude other pulmonary pathology like COPD. 2D ECHO was done in all patients and the presence or absence of PH was noted.

Statistical Analysis

Data were double entered using Microsoft Excel 2016 and analyzed using SPSS version 22. Data were summarized in frequency tables, pie charts, and histograms. Categorical variables were reported as a proportion. Continuous data were described as means (standard deviation) or medians (interquartile range) depending on the distribution of data. The T-test was applied in the following results whenever necessary. The level of significance criteria was selected at $P<0.05$.

Observations and Results

A total 171 patients with CKD of age>18 years admitted in the tertiary care hospital and research institute, were included in the study.Out of 171 patients' pulmonary hypertension was present in 67 (39.18%) patients with CKD.The majority of patients with PH were in the age group 41-50 years (55.38%) followed by 51-60 years (48.98%) with male predominance (61.19%) as shown in table 2.

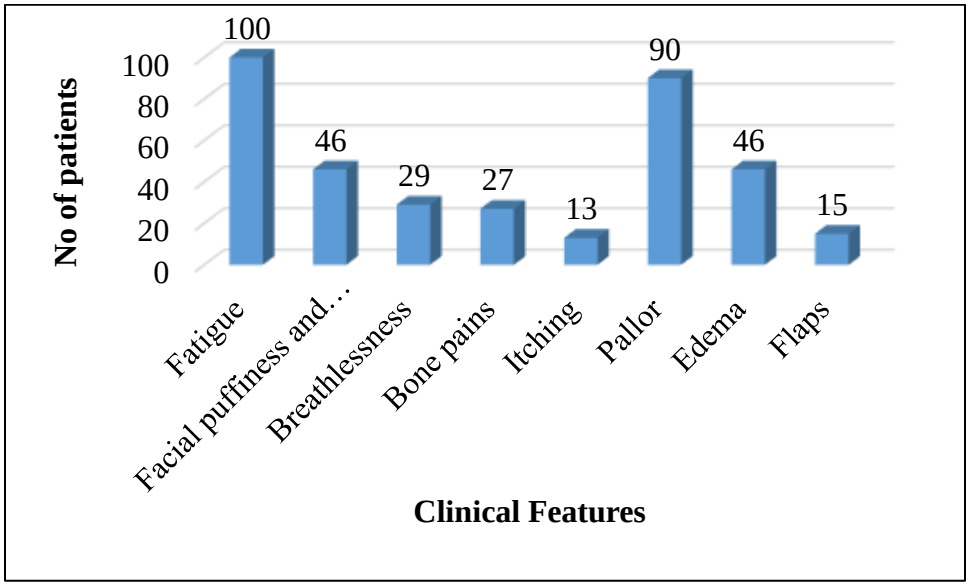
Table 2: Prevalence of PH according to age and sex

Demographic data		Pulmonary hypertension		Total	P-value
		Present	Absent		
Age group in years	<30	00	00	00	0.61(NS)
	31-40	06	25	31	
	41-50	29	36	65	
	51-60	24	25	49	
	>60	08	18	26	
Sex	Male	41	78	119	0.38(NS)
	Female	26	26	52	

From figure 1, it was observed that fatigue (58.47%) was the most common symptom and pallor (52.63%) was the most common clinical findings as comparable to others.

The mean systolic and diastolic blood pressure among patients was 147.51±9.74 mm of Hg and 88.97±4.64 mm of Hg respectively.

Figure 1: Distribution of patients according to clinical findings



Hypertension with Diabetes was found in most of the patients (40%) while 25.14% were having etiology of only hypertension.The majority of patients with PH were having etiology of combined diabetes mellitus with hypertension and showed statistical significance(P=0.03) as shown in table 3.

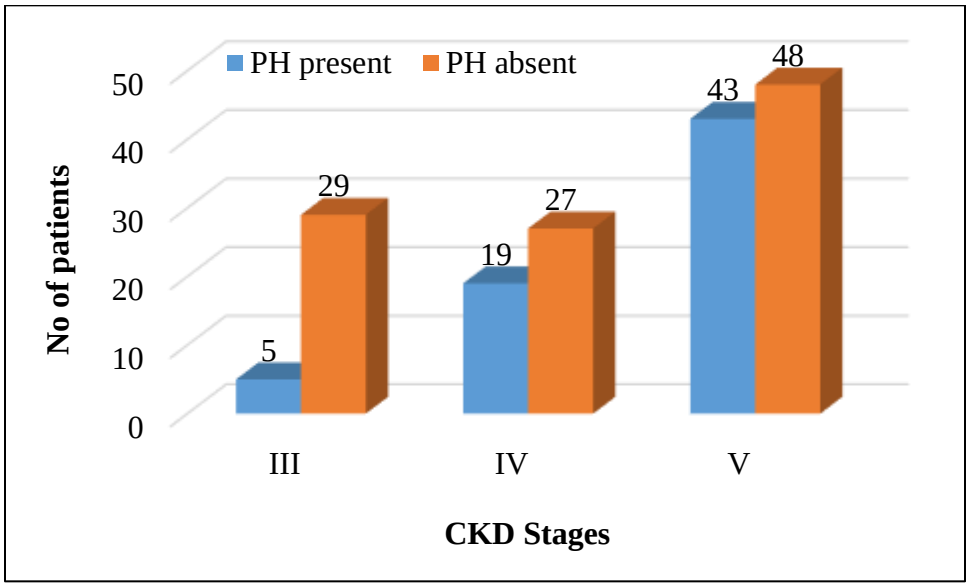
Table 3: Prevalence of PH according to etiology

Etiology	Pulmonary hypertension		Total	P-value
	Present	Absent		
Hypertension	12	31	43	0.21(NS)
DM + Hypertension	34	34	68	0.03 (S)
Diabetes Mellitus (DM)	00	06	06	-

Patients with duration of CKD >5 years (20 cases) had greater pulmonary hypertension compared to patients with duration <1 year (2 cases) with statistical significance(P=0.04).Patients with pulmonary hypertension had greater duration of hemodialysis (4.28±2.53) compared to patients without pulmonary hypertension (1.36 ±1.08) with high statistical significance, (P<0.001). However, patients with AV fistula had a greater number of PH(37 cases) compared to patients without fistula (30 cases) with high statistical significance, (P=0.005).

The maximum patients with PH (43) were in stage V CKD followed by 19in stage IV and 5 in stage III. This was statistically significant with P=0.01 as depicted in figure 2.

Figure 2: Relation of pulmonary hypertension according to the stage of CKD



Hemoglobin was significantly low in pulmonary hypertension patients with statistical significance, (P=0.003) as compared to other investigations, (p>0.05). Whereas low hemoglobin, high phosphorus, high ca-po4 product and high serum creatinine were significantly associated with stages of CKD, (P<0.05) as shown in table 4.

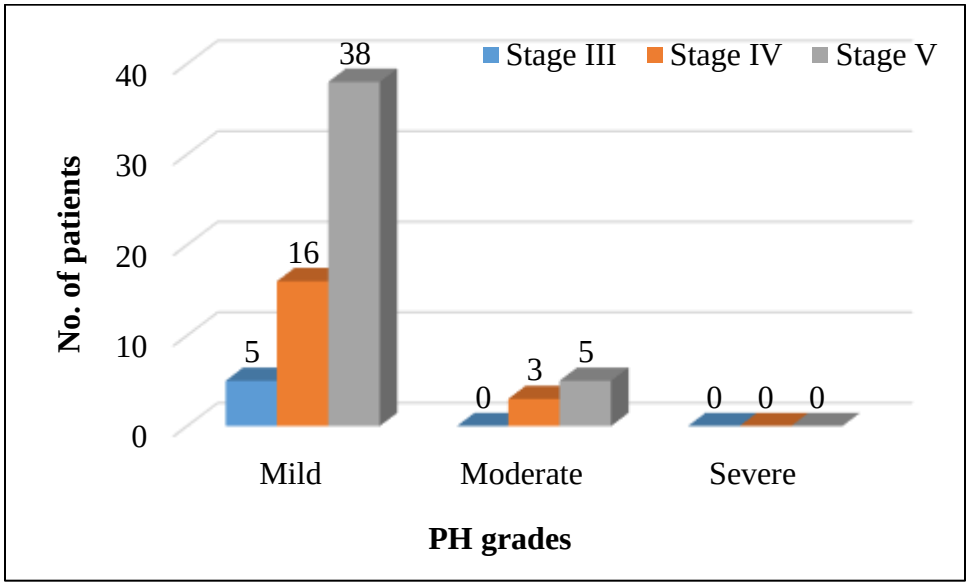
Table 4: Correlation of investigations with PH and stages of CKD patients.

Variables	Pulmonary Hypertension	Stages of CKD	P-Value

	Present	Absent	P value	III	IV	V	
Hb	7.31	9.78	0.003	9.68	8.65	7.21	0.002
Serum Calcium	8.27	8.51	0.32	8.67	8.32	8.11	0.32
Phosphorus	3.96	3.61	0.78	3.36	3.56	3.98	0.02
Ca-P04 Product	32.44	30.15	0.51	30.35	32.2	30.6	0.03
Serum Creatinine	6.89	5.88	0.31	4.23	5.11	6.98	0.001

From figure 3, it was observed that the patients with Stage V had more patients with moderate PH compared to patients with Stage III with moderate PH with statistical significance, (P=0.02).

Figure 3: Correlation between pulmonary hypertension grades and stages of CKD



Multivariate regression analysis was done by the enter method. The table shows a significant association of pulmonary hypertension with etiology of both DM + hypertension, duration of hemodialysis, AV fistula, and Stage of CKD, (Table 5).

Table 5: Multivariate Regression Analysis of Pulmonary hypertension

Variables	B	Std. Error	Wald	P value	OR	95% CI for OR	
						Lower	Upper

Age	0.394	0.315	1.560	0.212	1.483	0.799	2.752
Sex	0.256	0.277	0.857	0.354	0.774	0.450	1.331
Hypertension	0.860	0.281	9.338	**0.002**	2.363	1.361	4.102
DM	0.256	0.277	0.857	0.354	0.774	0.450	1.331
DM +Hypertension	0.935	0.284	10.822	**0.001**	1.393	1.093	2.685
Duration of CKD	1.723	0.283	15.391	**0.000**	7.324	4.168	9.543
Stage of CKD	1.219	0.295	17.042	**0.000**	2.296	1.166	3.527
Hemodialysis duration	1.921	0.265	52.597	**0.000**	6.830	4.063	11.479
AV fistula	1.264	0.243	27.160	**0.000**	3.540	2.201	5.695

Discussion

The present study shows mean age falling in the 5th decade (53.86±13.11years) with male predominance which is similar to the previous studies [8-10]. This high prevalence of CKD in male patients and in the elderly population may be attributable to a variety of different risk factors for CKD such as diabetes and hypertension in older individuals. However, the age-associated decline in kidney function may also be responsible for high rates of CKD in the elderly that is not explained by other known risk factors. The distribution of patients according to etiology of CKD showed that hypertension with Diabetes was found in 39.77% patients while 25.14% were having etiology of only hypertension, followed by Chronic glomerulonephritis (5.26%) and diabetes alone (3.51), and idiopathic (26.31%).Similar findings are observed by Morranne et al [9], Singh et al [11] and Tilman B et al [12].

It was observed that symptoms among 100(52.63%) patients had fatigue, while 46(26.9%) presented facial puffiness and edema. Breathlessness was observed in 29(16.95%) of the patients followed by bone pain 27(15.79%), itching 13(7.6%). Pallor was present in 90(52.63%) patients while 45(26.9%) were presented with edema. Uremic odour was observed in 18(10.53%) of the patients followed by flaps 15(8.77%). These findings are comparable with the study conducted by Singh S et al [11]. The mean systolic blood pressure among patients was 147.51±9.74 mm of Hg and mean diastolic blood pressure among patients was 88.97±4.64 mm of Hg which is in accordance with the study done by Sohal, et al [13].

The distribution of patients according to the stage of severity of CKD showed that stage V was found in 53.22% patients while 26.9% were in stage IV and 19.88% patients in Stage III. Thus, the present study shows an increased prevalence of CKD patients in stage V.MorranneO et al [9]and Agarwal AK et al [10] observed an increased prevalence in stages V and IV.

The mean hemoglobin among patients was 9.34±2.76 gm%. The mean serum calcium among patients was 8.42±1.05 mg/dl. The mean serum creatinine among patients was 6.27±4.01 mg/dl. The correlation between investigations and stages of CKD patients showed that hemoglobin, phosphorus, Ca-po4 product, and serum creatinine were significantly associated with stages of CKD. ($P<0.05$).No correlation was observed between stages of CKD and serum calcium, though it was found to be decreasing with higher stages, ($P>0.05$).These findings are comparable with the study conducted by Cases-Amenós A et al [14].

In the present study, the prevalence of PH was present in 67 (39.18%) patients with CKD, with mild, moderate, and severe accounting for 59%, 8%, and 0% respectively. The majority of patients with PH were in the age group 51-60 years (48.98%) as compared to 41-50 years (55.38%).There was no statistically significant association with respect to age and sex, ($P>0.05$) The majority of patients with PH were having etiology of diabetes mellitus with hypertension and showed statistical significance, ($P<0.05$). Patients with duration >5 years had greater PH compared to patients with duration <1 year with statistical significance, ($P<0.05$).The patients on hemodialysis had greater PH compared to patients, not on dialysis, ($P<0.05$)Patients with AV fistula had greater PH compared to patients without fistula with statistical significance, ($P<0.05$). The correlation between investigations and PH among CKD patients showed that hemoglobin was significantly low in PH patients with statistical significance, ($P>0.05$). The relation of PH according to the stage of CKD showed that patients with Stage V had a greater prevalence of PH (47.25%) compared to patients with stage III (14.7%) with statistical significance. ($P<0.05$). These findings are in accordance with the study done by Zhang Q et al [15], Mann A et al [16] and Mehta KS et al [17].

Patients with Stage V had more patients with moderate pulmonary hypertension compared to patients with Stage III with statistical significance, ($P<0.05$) which is comparable with the other studies [16-18]. However, the relationship between PH and CKD has been inconsistent so far. Another study conducted by YenigunE et al [19], showed that the prevalence of PH in patients with early-stage CKD was similar to those with stage 5 CKD and no significant difference was noted in PH in cases undergoing hemodialysis and those without hemodialysis. Pulmonary arterial hypertension is significantly associated in patients with CKD and an increase in severity of PAH occurs with deterioration of renal function in CKD cases.

Conclusion

The present study concludes that pulmonary hypertension is more prevalent in patients with chronic kidney diseases.As duration of CKD increases and PH was found to be more prevalent. However, the severity of pulmonary hypertension directly correlates with stages of chronic kidney diseases i.e., an increase in severity of PH occurs with deterioration of renal function in CKD cases.As a significant association was found between PH and CKD, active search for PH in CKD patients and its timely management at the initial stages can decrease morbidity and mortality resulting from PH. Also, more research work is required to evaluate other confounding risk factors, management strategies and prognosis of such patients, so as to decrease the morbidity and mortality resulting from PH in CKD patients.

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