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Original Research Article.

To Study Prevalence of Pulmonary Hypertension in Various Stages of Chronic Kidney Disease

Jatin Garg[1], RPS Sibia[2], Lovleen Bhatia[3], Sachin Kaushal[4], Chanderdutti[5], Icha Gupta[6]

[1,5]Senior Resident, [2]Professor and Head, [3]Professor, [4]Assistant Professor, [6]Junior Resident,
Department of Internal Medicine, Government Medical College and Rajindra Hospital, Patiala, Punjab, India.

ABSTRACT

Background: Pulmonary hypertension (PH) is a life-threatening condition with a poor prognosis if not treated. PH is found in patients of CKD due to increased volume overload, exposure of dialysis membranes and AV-Fistula.

Objectives: (1) The aim of this study was to determine the prevalence of Pulmonary Hypertension in the chronic kidney disease patients (2) To objectively evaluate the effect of stage of chronic kidney disease on severity of Pulmonary Hypertension.

Materials and Methods: The present prospective study was conducted on 100 patients. Detailed history and clinical examination were recorded. Transthoracic 2-D echocardiography was used to assess the severity of PH after proper categorization of patients according to stage of CKD.

Results: The prevalence of PH in the study population was 33%. Amongst these subjects according to the severity, 42.4% (14) had mild, 36.4% (12) had moderate and 21.2% (7) had severe PH. 68% (68) of patients belonged to stage 5 of CKD and 93.9% (31) of patients having PH were of stage 5 CKD only.

Conclusion: PH is seen in patients of CKD and there is high prevalence in ESRD (Stage 5) of CKD. There is a positive role of duration of CKD, duration of Hemodialysis, AV-Fistula on PH prevalence.

Keywords: PH, CKD, AV-Fistula, End Stage Renal Disease.

***Correspondence to:**

Dr. Sachin Kaushal,
Assistant Professor,
Department of Internal Medicine,
Government Medical College and Rajindra Hospital,
Patiala, Punjab, India.
drsachinkaushal@gmail.com

Abbreviations

AVF: Arteriovenous Fistula, **CKD:** Chronic Kidney Disease, **ECG:** Electrocardiogram, **eGFR:** estimated Glomerular Filtration Rate, **ESRD:** End Stage Renal Disease, **HD:** Hemodialysis, **PASP:** Pulmonary Artery Systolic Pressure, **PH:** Pulmonary Hypertension, **RAP:** Right Atrial Pressure, **TRV:** Tricuspid Regurgitation Velocity

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INTRODUCTION

Chronic kidney disease (CKD) is an important cause of long-term morbidity and mortality. CKD is an irreversible, progressive reduction in renal function. It is estimated that 1/3rd of patients with DM will develop nephropathy within 5 to 10 years after the diagnosis of diabetes and progress to End stage renal disease (ESRD). Hypertension is also a common cause, accounting for 1/3rd of patients.[1] Presence of evidence of renal involvement for a period of more than 3 months, together with eGFR less than 60 ml/min, the term CKD stage 3. In stage 4, eGFR is between 29 and 15 ml/min and in stage 5 is eGFR less than 15 ml/min or the patient is receiving renal replacement therapy.[1]

Pulmonary hypertension (PH) is a syndrome characterized by elevated pulmonary pressures. It is a life-threatening condition with a poor prognosis if untreated. The definition of PH is based upon right heart catheterization measurements. PH is defined as a mean pulmonary artery pressure greater than 25 mmHg at rest.[2] Risk factors for development of PH in CKD include arteriovenous fistula which lead to decrease in systemic vascular resistance, enhanced venous return and increased cardiac output.[3] Neutrophils get activated secondary to blood–dialysis membrane contact which is accompanied by reversible neutrophil sequestration in the lungs, a phenomenon that contributes to causing or worsening micro vascular lung disease in HD patients eventually leading to PH.[4-6]

Till date, only few studies have been done in the North - Indian population which have estimated the prevalence and its severity in CKD patients. There has been an alarming rise in the number of cases of CKD. In this study, an attempt was made to estimate the prevalence of PH in 100 CKD patients, the effect of stage of CKD on severity on PH.

OBJECTIVES

1. The aim of this study was to determine the prevalence of Pulmonary Hypertension in chronic kidney disease patients
2. To objectively evaluate the effect of stage of chronic kidney disease on severity of Pulmonary Hypertension.

METHODS

Study Design

A prospective study was conducted on 100 patients attending in-patient/out-patient department of medicine. All clinically diagnosed cases of chronic kidney disease were taken up for the study after application of the inclusion and exclusion criteria.

Inclusion Criteria

- All CKD stage 2 and above (as per K-DOQI guidelines (eGFR was calculated using the MDRD formula)
- Age group >18 years

Exclusion Criteria

- Pregnant females
- All known cases of PH (Primary & Secondary to left-sided heart diseases)
- Rheumatic heart diseases
- Valvular heart diseases
- Collagen vascular diseases
- HIV infection
- Pulmonary diseases (COPD, pulmonary embolism, and scleroderma).
- Failure to give informed consent.

All the patients underwent a detailed clinical evaluation, and findings were entered in a case record form. Medical history included age, gender, associated comorbidity, particularly diabetes and hypertension, CKD duration, dialysis and its duration, and presence or absence of AVF. Laboratory investigations like complete blood count, urine routine, blood urea, serum creatinine, serum potassium, serum calcium and phosphate, ECG and echocardiography were also done.

PASP was estimated as the sum of transtricuspid gradient and an estimation of RAP.[7] It is the application of Bernoulli equation to measure the tricuspid regurgitant jet velocity (TRV). This value should be added to the Right Atrial Pressure (RAP) and then PASP is then calculated: PASP = (4 x TRV squared) + RAP.[8]

Each CKD patient was staged on the basis of eGFR into various stages. According to classification, all the patients who were suffering from PH were also graded on the basis of Pulmonary Artery Systolic Pressure (PASP). PH was defined as PASP values ≥ 35 mmHg measured by Doppler echocardiography.[9,10] The severity of PH was categorized acc. to PASP ranging from mild (35 - 45 mmHg), moderate (45 - 60 mmHg) to severe (over 60 mmHg).[11] History sheets were collected regarding duration of CKD, HD and presence of AVF for every patient.

Statistical Analysis: At the end of the study period relevant statistical tools were used like mean ± SD, media and chi-square test. Values were considered to be statistically significant if p-Value < 0.05. Data was analyzed using the Statistical Package for Social Sciences (SPSS).

Table 1: Demographic Characteristics among patients having CKD with PH

Sr. No.	PARAMETERS	CKD WITH PH	CKD WITH NON – PH	P - VALUE
1.	Age (years)	53.97±15.11	56.0±13.63	0.501
2.	Gender (M/F)	18/15	36/31	0.939
3.	CKD Stage 3b	0	4	0.001
	CKD Stage 4	2	26	
	CKD Stage 5	31	37	

Table 2: Correlation of PH with Other Parameters

Sr. No.	PARAMETERS	CKD WITH PH	CKD WITH NON – PH	P - VALUE
1.	Duration of CKD (months)	20.15±8.82	8.25±8.25	0.001
2.	On Hemodialysis	97%	46.3%	0.001
3.	Duration of Dialysis (months)	11.91±7.39	4.06±7.17	0.001
4.	AV Fistula	63.6%	28.4%	0.001

Table 3: Correlation of CKD Stage with Severity of PH

CKD Stage	Mild	Moderate	Severe
3b	0.0% (0)	0.0% (0)	0.0% (0)
4	7.1% (1)	8.3% (1)	0.0% (0)
5	92.9% (13)	91.7% (11)	100.% (7)
P – Value		0.999	

RESULTS

Demographic Characteristics among patients having CKD with PH

In the present study, 100 cases of chronic kidney disease were taken. Patients having CKD with PH were of average age 53.97±15.11 years whereas 56.0±13.63 years in patients without PH. Patients with PH consisted of 54.5% (18) males and 45.5% (15) females, while patients having CKD without PH included 53.7% (36) males and 46.3% (31) females. Of the total patients having PH, 93.9% (31) were of stage 5 CKD and 6.1% (2) were of stage 4. (Table 1)

Correlation of PH with other parameters

The association of duration of CKD, modality of treatment, duration of HD, presence of AV-Fistula and co-morbidities with PH were studied. Mean duration of CKD in patients having PH was 20.15±8.82 months as compared to 8.25±8.25 months without PH. 97% (32) of patients having PH were obtaining treatment in the form of HD. The mean duration of HD in patients with PH was 11.91±7.39 months whereas 4.06±7.17 months in patients without PH. 63.6% (21) were using AV-Fistula for purpose of HD. (Table 2)

Correlation of CKD stage with Severity of PH

The present study didn't reveal any positive correlation between CKD stage and severity of PH (p value 0.999). (Table 3)

DISCUSSION

Pulmonary Hypertension (PH) is a progressive disorder associated and of paramount importance to study a strong independent predictor like PH which influences morbidity and. There are very limited Indian studies assessing the prevalence of PH in CKD patients. In patients with Stage 5 CKD, PH has been recognized to be a frequent condition and appears to be independent from cardiovascular disease prevalence.

In the present study, the mean age of patients having CKD with PH was 53.97±15.11 years and patients having CKD without PH was 56.0±13.63 years. Our findings were comparable with the studies performed by Singh NP et al.[12], Nakhoul F et al.[13], Fabbian F et al.[14] and Tudoran et al.[15] There is no effect of age on the prevalence of PH in our study and other studies also support our finding.

In our study, PH was found to be slightly more in males as compared to females. Yet there is no statistical significance of gender with PH and the similar result was seen in studies done by Etemadi J et al.[16], Nakhoul F et al.[13], and Fabbian F et al.[14] In contrast, the results of Mehta KS et al.[17] (more in males, p = 0.03) and Moniruzzaman M et al.[18] (male predominance) were in favor that gender has a significant association with PH. There's paucity of data describing the role of gender in pathogenesis of PH in CKD population.

The prevalence of PH in CKD patients in the present study was 33%, which is similar to study of Redkar et al.[19] The prevalence in study by Tarras et al.[20] was found to be as low as 26.74% and Moniruzzaman et al.[18] found it to be as high as 68.6%. The prevalence of PH has varied in medical literature because different definitions of PH might account for varying prevalence estimates. Yigla M et al.[21] reported the prevalence to be 29.1% when ePASP was more than ≥45 mm Hg. Prevalence estimates of Mehta et al.[18] and Hayati F et al.[22] was as high as 60.5% and 62.3% when PH definition ePASP used was ≥ 30 mm Hg and ≥ 25 mm Hg respectively.

PH was found after CKD stages 3b and above and severe PH was seen in around 68% of cases of ESRD (Stage 5). Our finding is concordant with the study done by Mehta KS et al.[18] where none of the subjects in CKD stage 2 revealed PH and 68.59% of patients were of CKD stage 5 had PH. PH gets aggravated by risk factors typical of CKD like volume overload, AVF, sleep disordered breathing, endothelial dysfunction, exposure to dialysis membranes, vascular calcification and stiffening and severe anemia.[23,24] Li Z et al.[25] also found the similar relation (p < 0.001). Another possible reason for the high prevalence of PH in Stage 5 CKD could be that patients report so late to healthcare facilities in their later stages of illness and by that time they need HD for the management of their condition.

As of now there are fewer studies correlating the CKD Stage with severity of PH. In the present study, we did not find any relationship between the stage of CKD and severity of PH. However, the maximum patients of mild, moderate and severe PH were having Stage 5 CKD.

Significant association was seen between CKD duration and PH prevalence (p 0.001) Studies performed by Mehta KS et al.[18], Havlucu et al.[26] and Patel et al.[27] also found the same correlation. The greater the duration of the CKD, the longer will be exposure of the patients to the altered cardiovascular physiology including synergistic effects of increased pulmonary vascular resistance, increased cardiac output, elevated PCWP, and hence, the chances of having more severe pulmonary hypertension increases.[23]

Nakhoul F et al.[13] in 2005 studied the role of Nitric Oxide (NO) and it's metabolites in the pathogenesis of PH where it was found that PH in patients on HD occurs because of uraemic-induced endothelial dysfunction and impaired production of NO. Longer the duration of CKD, the pulmonary vasculature becomes more incompatible to accommodate the AV-access mediated elevated cardiac output (CO) and subsequently cause PH.

Our study revealed statistically significant presence of PH in patients having CKD treated on HD. A study done by Mehta et al.[18] in 2019 showed statistically significant presence of PH in patients of CKD treated with HD (81.8%) (p < 0.001). However, lower prevalence of PH among patients on HD was seen in studies of Moniruzzaman et al.[18] (68.6%). and Kiykim et al.[28] (68.6%). Factors specific to HD like exposure to dialysis membrane and AV fistula contribute to pulmonary hypertension. Uremic patients on chronic HD therapy, via AV access exhibit decreased Nitric oxide (NO) production. This endothelial dysfunction, coupled with prolonged elevation of endothelin, reduces capacity of pulmonary circulation to maintain AV access mediated elevation of cardiac output and contributes to pulmonary hypertension.[23-25] It is also believed that microbubbles escaping from the dialysis circuit can trigger vasoconstriction and vascular sclerosis.[29,30]

There was a statistically significant association between duration of HD and prevalence of PH in the present study (p < 0.001). Other studies also support our findings showing similar findings including one done by Mehta et al.[18] showed patients with longer duration of HD had higher prevalence of PH. Tudoran et al.[15], Patel et al[27], Issa et al.[31] and Bozbas et al.[32] also found a similar association. Redkar N et al.[19] also concluded that duration of HD affects the development of PH.

In our study 33% of patients with CKD had PH and among them 63.6% (n = 21) of patients had Arterio-Venous Fistula (P value <0.001). Other studies having the similar association of AV fistula with PH are Mehta et al.[18], Havlucu et al.[26] The role of AVF has been studied in numerous studies including the one done by Nakhoul F et al.[13] where they observed a fall in PAP and cardiac output after temporary compression of AVF by 8 – 10 mm Hg and 13 mm Hg respectively. The AVF created causes decrease in the systemic vascular resistances with increase in venous return and cardiac output, which helps maintain proper blood flow to all organs and tissues. These adaptations increase pulmonary blood

flow and set the stage for PH. Well-performed studies show that pulmonary pressure increases in strict temporal relationship with AVF creation[33] and that PH tends to worsen over time in this population.[26,14]

STRENGTHS OF STUDY

This is the first study done on North-Indian Punjabi population to determine the prevalence of PH in the CKD population.

Our study is one of the fewer Indian studies analyzing the impact of CKD stage on severity of PH.

LIMITATIONS

In our study, we have relied only upon echocardiography for the determination of hemodynamic parameters and have not used any invasive methods to verify our results.

Another limitation was the small size of our study group because it was very difficult to find patients fulfilling the inclusion criteria.

CONCLUSION

Pulmonary Hypertension is a potentially serious and fatal outcome of chronic kidney disease. All the patients getting admitted should be screened for it and managed at the earliest possible to reduce the mortality.

1. ESRD or Stage 5 CKD patients are at the maximum risk of developing PH with highest prevalence so observed in our study.
2. Risk factors like mode of treatment via HD, AV-Fistula has a role to play in the pathogenesis of PH in CKD patients.
3. Longer the duration of CKD and HD, higher are the chances of patient developing PH.

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