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RENAL IMPAIRMENT ASSOCIATED WITH DIFFERENT PULMONARY ARTERIAL HYPERTENSION STAGES

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ABSTRACT

Background: An imbalance between the processes of vasoconstriction and vasodilation characterizes pulmonary arterial hypertension, a multiple pathobiology and complicated and interdisciplinary illness.

Aim: The objective of our research was to determine the prevalence of pulmonary arterial hypertension (PAH) in individuals with chronic kidney disease (CKD) and investigate the correlation between PAH and different phases of CKD.

Methods: A cross-sectional hospital-based study including 60 CKD patients was carried out between December 2020 and June 2022. With the use of 2D echocardiography, pulmonary arterial pressures were determined, and MS Excel was used to evaluate the results.

Results: Between CKD patients, the mean pulmonary artery systolic pressure (PASP) was 50.83 ± 9.779 mmHg, and the prevalence of PAH was 86.7%. The prevalence of PH increased as CKD stage advanced. Diabetes and hypertension had a strong association with PH (59.6% & 92.3%). Compared to individuals receiving conservative therapy, the prevalence of PH in hemodialysis (HD) patients (63.5%) was significantly higher. those on dialysis with an arterio-venous fistula had a pulmonary arterial pressure that was substantially greater (44.2%) ($p < 0.001$) than those using a femoral or jugular vein HD catheter.

Conclusion: Individuals with chronic kidney disease had a notable incidence of PAH. When compared to patients who used a femoral or jugular vein HD catheter, patients undergoing dialysis via an arterio-venous fistula exhibited noticeably elevated pulmonary arterial pressures. The most frequent etiological variables for chronic renal disease in our research were diabetes and hypertension.

Keywords: PAH/PH (Pulmonary Arterial Hypertension), CKD (Chronic Kidney Disease), HD (Hemodialysis)

INTRODUCTION

The term "orphan disease" refers to the fact that pulmonary arterial hypertension is a complicated and interdisciplinary problem that affects a small number of people and is often disregarded by healthcare systems and medical practitioners. The development of right heart catheterization procedures has led to a considerable improvement in our understanding of

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cardiac and pulmonary hemodynamics, which has eventually enhanced our understanding of illness and allowed for more informed patient care. A multifactorial pathobiology of PH includes thrombosis, cellular proliferation, remodeling of the pulmonary artery walls, and an imbalance between vasoconstriction and vasodilation mechanisms. These factors ultimately lead to an increase in pulmonary vascular resistance.[1]

Chronic kidney disease (CKD) is a global public health concern that is now experiencing an epidemic. Compared to all other chronic non-infectious illnesses, chronic kidney disease (CKD) allows patients to enjoy their lives even while they are terminally ill. Cardiovascular disease is one of the leading causes of death for people with end-stage renal failure. They are typically impacted by this ailment even prior to reaching stage 5. [2] The length of artificial life extension (by transplantation or RRT) is closely correlated with the patient's or his provider's financial means. Patients with end-stage renal disease (ESRD) still have high morbidity and death rates, even with the tremendous advancements in ESRD therapy. Between fewer than 10% and more than 50% of ESKD patients have been observed to have PH.[3–16] The vast variation is mostly related to the methods of diagnosing PH (catheterization versus echo/Doppler), the unpredictability of diagnostic standards, and the existence or lack of symptoms.[15] People with end-stage renal disease, especially those receiving hemodialysate, are more likely to have their pre-existing pulmonary hypertension deteriorate. One specific risk factor that might exacerbate pulmonary hypertension is the existence of an arterio-venous access (4, 6, and 33). Anemia, hyperparathyroidism, hyperphosphatemia, increased FGF-23, and widespread inflammation are the main risk factors associated with chronic kidney disease (CKD). The conventional risk factors of dyslipidemia, hypertension, hypervolemia, and sympathetic hyperactivity are also present.
Many regulatory proteins limit the process of vascular calcification.
Deficiency of these proteins can be seen in the setting of CKD and end-stage kidney disease, leading to vascular calcification. Calciprotein particles (CPPs): Made up of chaperone-binding proteins and calcium phosphate crystals, CPPs are circulating particles. At healthy serum calcium and phosphate concentrations, these chaperone-binding proteins prevent calcium-phosphate from crystallizing in the blood. The main chaperone-binding protein in CPPs is fetin A; other essential components include albumin and other plasma proteins. Calcium phosphate can precipitate when fetuin A concentration is lower.
Research has demonstrated a correlation between reduced levels of fetuin A in the blood and increased vascular calcification in dialysis patients. Early detection of the problem's scope, or PH in CKD/ESRD, allows for the appropriate implementation of interventions aimed at reducing cardiovascular mortality and morbidity. Data on the prevalence of PH in patients with chronic kidney disease (CKD) in India are few.
In this study we wanted to evaluate pulmonary arterial hypertension as a predictor of severity of chronic kidney disease and correlation with its various stages, estimate the frequency of pulmonary arterial hypertension in patients with chronic kidney disease and correlate the relationship between pulmonary arterial hypertension and stages of chronic kidney disease.

MATERIALS AND METHODS

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This was a cross-sectional research carried out in a hospital setting with 60 patients who visited the tertiary care hospital's outpatient department (OPD) and had been diagnosed with chronic kidney disease (CKD). The study was approved by the institutional ethics committee and the participants provided written informed permission.

All patients with stage 2 and later chronic renal disease in accordance with KDOQI standards, age older than eighteen years were include in the study.

Individuals with a history of COPD, ILD, pulmonary arterial hypertension, sleep apnoea, Thrombotic pulmonary embolism, Kidney Injury, Acute, Severe diseases, HIV, Individual with left-sided cardiac disease-related PAH, Kidney polycystic disease, Sepsis and burns, pregnancy were excluded from the study.

MS Excel 2010 was used to enter the data, and SPSS version 24's ANOVA was used to analyze it. Standard deviation, mean, and percentage were used as descriptive statistical metrics. The Z test and Chi square/Fisher's exact probability test were used as inferential statistical tests. Pearson's correlation tests were used to determine the difference in proportions. At $p<0.05$, associations and differences were considered statistically significant. Tables with the data were displayed.

RESULTS

The majority of individuals were found to be between the ages of 51 and 60, then 61 years and older. There was a 51.67 ± 14.9 year old mean. Table 1 illustrates that men made up the bulk of the subjects.

It can be observed that, majority of subjects with PAH were in stage VD (stage V on dialysis) of CKD followed by stage 4. There is a statistically significant correlation between PAH and CKD stage. It is evident that 55.0% of CKD patients were using HD. It was discovered that there is a statistically significant correlation between HD and PAH. It is noted that AVF was present in 44.2% of CKD patients. Table 2 indicates that there is a statistically significant correlation between AVF and PAH.

Observations show that among patients with PAH, hypertension, diabetes, diabetic retinopathy, and hypertensive retinopathy, respectively, affected 92.3%, 59.6%, 23.1%, and 25% of cases. There is a statistically significant correlation between hypertension, diabetes, diabetic retinopathy, diabetic nephropathy, hypertensive retinopathy, and PAH. Of the 52 PAH patients, 33 were receiving hemodialysis. Every hemodialysis patient suffered from PAH. HD was started on 48.5% of PAH participants, and 42.4% of them were on it twice a week after that.

Table 3 indicates that there was no statistically significant correlation found between the prevalence of HD and the severity of PAH.

DISCUSSION

Beyond the pulmonary circulation, the pathogenesis of PH frequently involves chronic renal illness, right ventricular (RV) dysfunction, overactivation of neurohumoral signaling pathways, and several other processes that compromise overall cardiovascular fitness and function.

About 86.7% of the participants in our research had pulmonary arterial hypertension. The PASP averaged 50.83 ± 9.779 mmHg. Study by Suresh H et al[9] on pulmonary hypertension

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in different phases of chronic kidney disease (CKD) comprised 200 patients; the mean PASP was 38.52 ± 7.32 mmHg, and 60.5% of the patients had PAH.

In the Karnataka investigation by Suresh et al[9] and Mann A et al,[10] the mean PASP was 51.1 ± 13.3 mm HG and the prevalence of PAH was 43.5%. 108 CKD patients who were receiving regular follow-up and had their PH severity evaluated at the end of the third and sixth month were included in the research.

Reque and colleagues found that among patients with non-dialysis chronic kidney disease, the prevalence of PAH was 26%. The study analyzed 353 individuals who were in stage 3-5 of CKD. The authors of the study by Mann A et al[10] estimated the pulmonary arterial pressures of the 58 patients who were receiving dialysis through an AV fistula or peritoneal dialysis. The study examined the prevalence of pulmonary arterial hypertension in end-stage renal disease (ESRD). With a mean PASP of 44 ± 7 mmHg, the prevalence of PAH was 39.7%.

According to our research, PAH was more common in CKD patients, with a peak frequency of 48.3% ($p<0.001$) in stage VD. About 9.91%, 21.48%, and 68.5% of the participants in the third, fourth, and fifth stages of CKD had PH, according to a study done by Navaneethan SD et al.[11] Our study's outcomes were comparable to these.

The majority of individuals with CKD stages 3 and 4 in a research by Suresh et al. had mild to moderate pulmonary hypertension. Stage 5 patients, on the other hand, had significant pulmonary hypertension. Due to the extremely small number of patients recruited in stages 3 and 4, this finding did not show to be a substantial reason for worry.

In a New Delhi observational research by Mann et al.[10] individuals with CKD stages IV (38%), V (84%), and VI had considerably higher pulmonary arterial pressures. Similar conclusions were reached in a research by Navaneethan SD et al.[11] which used an American population. The bulk of the patients in our research were male, with a mean age of 51.67 ± 14.9 years.

Our study's findings (p value=0.772, p=0.550) did not show a statistically significant association between pulmonary arterial pressures and age or sex. These findings aligned with the findings of Raymond TE et al.[12]

The conduit pulmonary arteries gradually lose their flexibility beyond the age of 35, while the medium and small vessels become more muscularized. This is typified by the deposition of collagen and the degradation of elastin, which together result in vascular stiffness and modest fibrotic remodeling of the intima. The major pulmonary artery dilates somewhat with age, and the average mean mPAP and PVR slightly increase as a result of these age-related morphological and histologic changes. These changes are most noticeable in the seventh decade of life and beyond.

The research done by Raymond TE et al[12] (p=0.003), Kovacs G et al[13] (p=0.002), and Patel P et al[14] ($p<0.05$) revealed a significant correlation between the length of CKD and the prevalence of PH. While 48.1% of patients in our research with CKD for longer than a year also had PH, there was no statistically significant correlation established between the length of CKD and PH. ($p = 0.199$). The limited sample size is the likely cause.

Comorbidities, especially heart illness, are very prevalent in individuals with ESKD, which may account for the population's higher-than-usual prevalence of PH. Uncertainty surrounds

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the pathogenic role in the actual development of PH. Of the 60 individuals in our research, 52 had PAH.

Of 60 patients, 33 (55%) were receiving HD, with the remaining patients receiving conservative care. Pulmonary hypertension affected every HD patient (63.5%). 42.4% of PAH individuals were on twice-weekly dialysis after 48.5% of subjects were started on HD. Therefore, there was a statistically significant ($p<0.001$) prevalence of PH in individuals receiving HD.

Studies by Patel P et al[14] and Mann et al[10] showed comparable outcomes ($p<0.001$).It is clear from the statistics above that patients on HD have a markedly increased risk of developing pulmonary arterial hypertension.

Renal replacement therapy and uraemia have important influence on the production of pro-inflammatory cytokines and oxidative stress. These circumstances raise the adhesion molecules on a variety of cells, which in turn raises the synthesis of substances that promote inflammation. Nitric oxide generation is reduced in end-stage kidney disease (ESKD) patients, which can lead to vasoconstriction and hypertension. An endogenous NO inhibitor, asymmetric dimethyl arginine (ADMA), is markedly elevated in ESKD.

Thirty-three of the 52 PAH patients received hemodialysis. Every hemodialysis patient suffered from PAH. 42.4% of individuals with PAH underwent twice-weekly dialysis after 48.5% began HD. Because there were so few patients receiving thrice weekly dialysis, there was no statistically significant correlation seen in our study between the frequency of HD and the severity of PAH. A study conducted by Hörl WH et al[15] revealed that the prevalence of PH was not significantly different between individuals who had twice and thrice weekly HD. In our study 33 patients were on haemodilysis, out of which 23 patients (38.3%) had AVF. All the patients having an AVF had significantly elevated pulmonary arterial pressures i.e. 23 out of 52 patients (44.2%, $p<0.001$).

When we compared the statistics of our study to those of Mehta et al. (p value=0.002), Antoniades C et al[16] (p value <0.05), and Mann et al[10] (p=0.001), we found many similarities. Thus, AVF plays a major role in the development of PH in CKD patients on HD; worsening of pre-existing PH was also noted in some of the aforementioned investigations.

In dialysis patients with end-stage kidney disease (ESKD), the occurrence of AV access flow has been connected to the development of PH. The development of PH is thought to be caused by an increase in vascular flow in the presence of pathological and hormonal alterations.

Diabetic nephropathy was seen in 14 (34%) of the diabetic individuals. Every diabetic nephropathy patient had elevated blood pressure in their lungs. Our study's data exhibits a substantial correlation with data from an Indian registry that lists diabetes and hypertension as the two most frequent causes of chronic kidney disease (CKD).

Similar to our analysis, investigations by Juonala M et al[17] found that the primary causes of chronic kidney disease were hypertension and diabetes mellitus. It is challenging to evaluate the data and provide trustworthy conclusions due to the tiny research population. Nonetheless, the researchers can get more precise results with more investigations.

Patients with stage 1 or stage 2 chronic kidney diseases were not included in the study population. Moreover, those who had peritoneal dialysis were not included. The diagnosis of

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PH was based on the indirect echocardiographic measures of PA systolic pressure and not on the right heart catheterization procedure.

CONCLUSION

According to the study, individuals with CKD had a noticeably greater frequency of PAH. The greatest degree of PAH was seen in individuals with CKD stage VD, and as CKD progressed, the severity of pulmonary hypertension dramatically increased. PAPs were substantially greater in patients receiving dialysis via an arterio-venous fistula than in those receiving HD catheterization from the jugular or femoral vein. Finally, no positive association between the duration of CKD and pulmonary hypertension was found.

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TABLES

Demographic	Subgroup	Frequency	Percentage
	<30	6	10.0
	31-40	11	18.3
	41-50	6	10.0
	51-60	20	33.3
	61 and above	17	28.3
Gender	Female	18	30.0
	Male	42	70.0
	Total	60	100.0

Table 1: Demographic Distribution

Stage	Subgroup	PAH		Total	X^2	P
		Absent	Present			
CKD	IIIB	6 (75.0)	1 (1.9)	7 (11.7)	37.74	0.001
	IV	2 (25.0)	12 (23.1)	14 (23.3)		
	V	0 (0.0)	10 (19.2)	10 (16.7)		
	VD	0 (0.0)	29 (55.8)	29 (48.3)		
	Total	8	52	60		
Hemodialysis	No	8 (100.0)	19 (36.5)	27 (45.0)	11.282	0.001
	Yes	0 (0.0)	33 (63.5)	33 (55.0)		
	Total	8	52	60		
Arterio-venous Fistula	No	8 (100.0)	29 (55.8)	37 (61.7)	11.282	0.001
	Yes	0 (0.0)	23 (44.2)	23 (38.3)		
	Total	8	52	60		

Table 2: **Relationship between stages of CKD and PAH**

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Comorbidities	PAH Present (52)	Total	p
Hypertension	48 (92.3)	56	0.001
Diabetes Mellitus	31 (59.6)	42	0.001
Mesangioproliferative glomerulonephritis	3 (5.7)	3	0.983
CIN	8 (15.4)	8	0.782
Diabetic retinopathy	12 (23.1)	14	0.038
Hypertensive retinopathy	13 (25.0)	17	0.041
Hypothyroidism	1 (2.0)	1	0.874
FSGS	2 (4.0)	2	0.991
Diabetic nephropathy	14 (27.0)	14	0.046

Table 3: Association between etiology of CKD and PAH