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Study of Prevalence of Pulmonary Hypertension Among Non-Dialysis and Dialysis Dependent Chronic Kidney Disease Patients

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Abstract
Hemodialysis is associated with development of pulmonary hypertension (PH). However, maintenance dialysis has extended the lives of hundreds of thousands of patients with CKD worldwide. It is important to detect the presence of pulmonary hypertension among patients undergoing hemodialysis, this is because CKD per se has increased cardiovascular morbidity and mortality; but the genesis of pulmonary hypertension as a consequence of hemodialysis (a mode of RRT) will have summation effect on the cardiovascular complications, thus reducing the life span of these patients. Further, detecting the presence of PAH among patients secondary to RRT who are due for transplantation will guide us about the overall prognosis in the post-transplant period. The data regarding PAH among patients with long term hemodialysis from India is sparse; hence this study was conducted with the objectives to determine the prevalence of pulmonary hypertension and to determine the factors predisposing to pulmonary hypertension among non-dialysis and dialysis dependent chronic kidney disease patients. Case Control study was be conducted among 100 non-dialysis and 100 dialysis dependent chronic kidney disease patients at Department of Nephrology, Mysore Medical College and Research Centre, Mysuru during July 2023 to December 2023. CKD Patients undergoing dialysis, aged >18 years, Chronic kidney disease stage 1-4 and Chronic kidney disease stage 5 (NDD and Dialysis Dependent). CKD patients receiving conventional management. Data was collected using pre-designed Proforma consisting of demographic profile, clinical profile, investigation profile and dialysis profile. Chronic kidney disease staging was based on the GFR values that is obtained by CKD-EPI formula. Chi-square test and ANOVA Test was used as test of significance. p value <0.05 was considered as statistically significant. Majority of cases were in the age group 41-50 years (26%) and majority of controls were in the age group 61-70 years (28%), majority of subjects were males in both groups, most common complication in both groups was Diabetes with Hypertension. Among cases, 94% were undergoing Hemodialysis and 6% were undergoing peritoneal dialysis. On 2D ECHO, in cases, 80% had Pulmonary HTN, 10% had Concentric LVH and in Controls, 9% had Pulmonary HTN, 30% had Concentric LVH. CKD patients on Dialysis had significantly higher percentage of Pulmonary HTN compared to CKD patients without Dialysis. Mean duration of Dialysis among subjects with Mild Pulmonary HTN was 14.35 ± 6.4 months, among subjects with moderate Pulmonary HTN was 23.85 ± 12.56 months and among subjects with severe Pulmonary HTN was 25.00 ± 14.5 months. From the study it was found that prevalence of pulmonary hypertension is high among patients on dialysis than those on conservative management. Among dialysis group, hemodialysis patients had high prevalence as compared to peritoneal dialysis (PD).

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Key Words
Pulmonary hypertension, chronic kidney disease, dialysis, conservative management, hemodialysis

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INTRODUCTION

Hemodialysis is associated with development of pulmonary hypertension (PH) which is estimated to be around 17-56%[1]. Normal pulmonary artery pressure at sea level has a peak systolic value of 18-25 mmHg. Definite pulmonary hypertension is present when pulmonary artery systolic and mean pressures exceed 30 and 20mmHg, respectively. Pathogenesis of renal failure associated with PH is complex and it may include metabolic and hormonal derangements, high cardiac output due to arterio-venous fistula (AVF), impaired endothelial function, anemia, fluid overload, and other factors. Impaired lung function and exercise capacity are commonly observed in patients with chronic renal failure[2,3]. Such limitations are due to several factors, including inflammation, myopathy, neuropathy, metabolic acidosis.

However, maintenance dialysis has extended the lives of hundreds of thousands of patients with CKD worldwide. Clear indications for patients with CKD include uremic pericarditis, encephalopathy, intractable muscle cramps, anorexia and nausea not attributable to reversible causes such as peptic ulcer disease, evidence of malnutrition and fluid and electrolyte abnormalities, principally Hyperkalemia that is refractory to other measures[4]. It is important to detect the presence of pulmonary hypertension among patients undergoing hemodialysis, this is because CKD per se has increased cardiovascular morbidity and mortality, but the genesis of pulmonary hypertension as a consequence of hemodialysis (a mode of RRT) will have summation effect on the cardiovascular complications, thus reducing the life span of these patients[5,6,7]. Further, detecting the presence of PAH among patients secondary to RRT who are due for transplantation will guide us about the overall prognosis in the post-transplant period. The data regarding PAH among patients with long term hemodialysis from India is sparse, hence this study was conducted with the objectives to determine the prevalence of pulmonary hypertension and to determine the factors predisposing to pulmonary hypertension among non-dialysis and dialysis dependent chronic kidney disease patients.

MATERIAL AND METHODS

Case Control study was be conducted among non-dialysis and dialysis dependent chronic kidney disease patients at Department of Nephrology, Mysore Medical College and Research Centre, Mysuru during July 2023 to December 2023.

Case: CKD Patients undergoing dialysis, aged >18 years, Chronic kidney disease stage 1-4 and Chronic kidney disease stage 5 (NDD and Dialysis Dependent).

Controls: CKD patients receiving conventional management.

Sample Size: Was estimated based on the difference in proportion of Pulmonary HTN between Dialysis CKD patients at 41.53% and Non-Dialytic CKD patients at 22.72% from the study by Magdy M. Emara *et al., et al*.[1] Using these values in the below mentioned formula sample size was 96 at 5% alpha eroor and 80% power and it was rounded off to 100 in each group. $N=2\ P\ (1-P)\ (Za/2 + Zß)2\ /(p1-p2)$[2].

Collection of Data: Chronic kidney disease patients those are non-dialysis and dialysis dependency at Department of Nephrology, Mysore Medical College and Research Centre, Mysuru from Data was collected using pre-designed Proforma consisting of demographic profile, clinical profile, investigation profile and dialysis profile. Chronic kidney disease staging was based on the GFR values that is obtained by CKD-EPI formula. The etiology of CKD was studied. The mode of dialysis and duration of dialysis was documented. The access for hemodialysis was noted. All the patients underwent complete hemogram, renal function tests, ultrasound abdomen, chest radiograph and 2D Echocardiogram. Two dimensional (2D) guided M-mode echocardiogram was performed with digital cardiac ultrasound machine. On dialysis patients it was done in the post dialysis day as it allows to control volume state of the patient since it is associated with least intra vascular volume. Pulmonary artery systolic pressure was recorded by tricuspid regurgitation jet method. Based on the pulmonary artery pressure, they were classified into three groups of mild degree (25-35mmhg), moderate (35-50mmhg) severe degree (>50 mmhg).

Statistical Methods: Data was analyzed using Epi Info version 7.2. Categorical data was represented in the form of Frequencies and proportions. Continuous data will be represented as mean and standard deviation. Chi-square test or Fischer's exact test [If Chi-square test is invalid] was used as test of significance for Categorical data. ANOVA test to compare mean between three or more groups. $p<0.05$ was considered as statistically significant.

RESULTS AND DISCUSSIONS

In the study 100 cases (Dialysis dependent CKD patients) and 100 controls (Non-dialysis dependent CKD patients) were included. Majority of cases were in the age group 41-50 years (26%) and majority of controls were in the age group 61-70 years (28%), majority of subjects were males in both groups, most common complication in both groups was Diabetes

Table 1: General Profile of subjects in two groups

		Cases (n = 100)		Controls (n = 100)		
		Count	percentage	Count	percentage	p-value
Age	<40 years	22	22%	14	14%	
	41-50 years	26	26%	20	20%	
	51-60 years	22	22%	26	26%	0.3529
	61-70 years	22	22%	28	28%	
	>70 years	8	8%	12	12%	
Sex	Male	65	65%	70	70%	
	Female	35	35%	30	30%	0.4503
Etiology of CKD	DM and HTN	50	50%	58	58%	
	HTN	44	44%	34	34%	
	Chronic Glomerulonephritis	4	4%	8	8%	0.1572
	Chronic Pyelonephritis	2	2%	0	0%	
Mode of Dialysis	Hematolysis	94	94%	0	0%	-
	Peritoneal Dialysis	6	6%	0	0%	
	Conservative Management	0	0%	100	100%	
Durationofdialysis (mean ± SD) [Months]		19.32 ± 15.52		-	-	
Haemoglobin (gm%)		8.67 ± 1.44		9.33 ± 1.08		0.0003*

Table 2: Pulmonary HTN in cases and controls

		Cases (n = 100)		Controls (n = 100)		
		Count	percentage	Count	percentage	p-value
2D ECHO	Pulmonary HTN	80	80%	9	9%	<0.001*
	Concentric LVH	10	10%	30	30%	
	Normal	10	10%	61	61%	

Table 3: Relationship between Pulmonary HTN and Duration of Dialysis

Severity of Pulmonary HTN	Duration of Dialysis (months) Mean ± SD	F Value	p-value
Mild (n = 20)	14.35 ± 6.4	5.212	0.007*
Moderate (n = 48)	23.85 ± 12.56		
Severe (n = 12)	25.00 ± 14.5		

ANOVA test

Table 4: Pulmonary HTN with respect to Mode of Dialysis in Dialysis dependent CKD

		Pulmonary HTN	
		Count	percentage
Mode of Dialysis in Dialysis dependent CKD	Hemodialysis (n = 94)	78	82.9%
	Peritoneal Dialysis(n =6)	2	33.3%

with Hypertension. Among cases, 94% were undergoing Hemodialysis and 6% were undergoing peritoneal dialysis, duration of dialysis among cases was 19.32±15.52 months. Mean Hemoglobin among Cases was 8.67±1.44gm% and among controls was 9.33±1.08gm%. There was significant difference in Hemoglobin levels between cases and controls.

On 2D ECHO, in cases, 80% had Pulmonary HTN, 10% had Concentric LVH and in Controls, 9% had Pulmonary HTN, 30% had Concentric LVH. CKD patients on Dialysis had significantly higher percentage of Pulmonary HTN compared to CKD patients without Dialysis (Table 2).

Severity of Pulmonary HTN: Outofthe80dialysisdependentpatientswithpulmonary hypertension,20(25%) had mild,48(60%) had moderate and 12(15%) had severe pulmonary hypertension.

Out of 9 Non-dialysis dependent patients with pulmonary hypertension, 7 (77.8%) had mild Pulmonary HTN and 2 (22.2%) subjects had moderate pulmonary hypertension.

Mean duration of Dialysis among subjects with Mild Pulmonary HTN was 14.35±6.4 months, among subjects with moderate Pulmonary HTN was 23.85±12.56 months and among subjects with severe Pulmonary HTN was 25.00±14.5 months. There was significant difference in duration of dialysis with respect to severity of Pulmonary HTN (Table 3).

Among subjects with Dialysis dependent CKD, 94 subjects were undergoing hemodialysis, of them 82.9% had Pulmonary HTN and among 6 subjects who were undergoing peritoneal dialysis, 33.3% had Pulmonary HTN (Table 4).

Pulmonary hypertension (PH) is highly prevalent in end stage renal disease. Many studies have confirmed this. The pathogenesis of PH in this population remains poorly understood. Reported associations include arteriovenous fistulae, cardiac dysfunction, fluid overload, bone mineral disorder and non-biocompatible dialysis membranes. Due to small numbers and cross-sectional nature of majority of studies no consistent association with any particular risk factor has been demonstrated. Further, little is known about impact of 'uraemic vasculopathy' on pulmonary vasculature. Hence there is a need for

better understanding of natural history and the pathogenesis of the condition which would help to individualise treatment of PH in end stage renal disease. In this study, an attempt was made to study the prevalence of pulmonary hypertension and probable etiology among CKD patients attending our hospital who were non-dialysis and dialysis (hemodialysis and peritoneal dialysis) dependent. Patients undergoing PD were on Continuous Ambulatory Peritoneal Dialysis (CAPD).

Among 100 dialysis patients, 94 were on hemodialysis and 6 were undergoing CAPD. Patients undergoing hemodialysis had access through arteriovenous fistula (AVF).

The mean age of patients in the dialysis group was found to be 53.04 years and was 60.8 years in the study done by Nakhoul F *et al*[8] in the non-dialysis group, mean age was 56.95 years. There was Age and gender matching in the present study.

Considering the etiology of CKD patients, it was found that 50% of patients had diabetes mellitus plus hypertension as the cause which is comparable to

The study done by Esam H *et al* where he found that both these factors contributed to 65% as an etiology for CKD[9]. Among the dialysis dependent patients included in our study diabetes plus hypertension contributed to 44%, as an etiology which is comparable to the study done by M. Yigla *et al*[10] that is 42.5%. Chronic glomerulonephritis and chronic pyelonephritis as an etiology were seen in 4% and 2% of CKD patients, it was comparable to the study done Alhamad EH *et al*[9] and Emara MM *et al*[1]. As compared to the last two factors, diabetes mellitus and hypertension ranks the list as common cause of CKD worldwide.

Among the dialysis dependent patients those were included in the study, the minimum and maximum duration of dialysis is 4 and 72 months respectively with mean of 19.32±15.52, whereas in the study done by P. Patel *et al* the minimum duration was 10 months and maximum duration was 50 months[12].

The mean hemoglobin level among cases was 8.67±1.44 gm%, among controls was 9.33±1.08% , this was similar to the observations in the study done by GK Modi *et al*[11] and P. Patel *et al*[2] which was 9.1gm% and 10gm% respectively.

2D Echocardiogram was done in all 200 CKD patients, 71 subjects were within normal limits, 89 patients had pulmonary hypertension of varying degrees and remaining 40 patients had concentric left ventricular hypertrophy (LVH) whereas in the study done by Shivendra S *et al* LVH was seen in 48% patients[12]. Further, CKD patients on Dialysis had significantly higher percentage of Pulmonary HTN compared to CKD patients without Dialysis ($p<0.01$). This was comparable to the study done by P. Patel *et al*[2].

Outofthe80dialysisdependentpatientswithpulmonaryhypertension, 20 (25%) had mild,48 (60%) had moderate and 12 (15%) had severe pulmonary hypertension.

Out of 9 Non-dialysis dependent patients with pulmonary hypertension, 7 (77.8%) had mild Pulmonary HTN and 2 (22.2%) subjects had moderate pulmonary hypertension. Similar high prevalence of pulmonary hypertension among hemodialysis patients was found in studies by P. Patel *et al*,[2] Mahdavi-Mazdeh M *et al*,[13] who found that PH among hemodialysis patients was 51.6%, 40% of patients on HD with A-V fistula had pulmonary hypertension as shown in the study done by Yigla M *et al*[4]. 82.9% of patients receiving HD among cases had pulmonary hypertension as evidenced in the study done by Seyed A *et al*[14]. Pulmonary hypertension was found in 30.6% of patients on hemodialysis in the study done by Yoo HH *et al*[15]. 39% of patients had pulmonary hypertension undergoing HD as seen in cross sectional study done by Fabio F *et al*[7]. 28(48%) of 42 HD patients had pulmonary hypertension as evidenced in the study done by Nakhoul F *et al*.[8] A high prevalence of pulmonary hypertension was demonstrated among 41.53% patients receiving hemodialysis as shown in study done by Emara MM *et al*.[1]

In the present study out of 6 cases who underwent Peritoneal Dialysis, 2 subjects (33.33%) had PHTN. In the study done by Kumbar L *et al*[16] prevalence of PH was 42% among PD patients. Therefore, as compared with hemodialysis patients, prevalence of PH is much less in CAPD patients which is comparable with study done by P. Patel *et al*[2].

All the patients undergoing hemodialysis those were included in the study had AVF access and low hemoglobin levels, which probably could be the reason for high prevalence of PH among these patients, along with other factors like lower Hematocrit, serum bicarbonate and higher serum creatinine levels, which was also seen in the study by Nakhoul F *et al*.[8]

CONCLUSION

From the study it was found that prevalence of pulmonary hypertension is high among patients on dialysis than those on conservative management. Among dialysis group, hemodialysis patients had high prevalence as compared to peritoneal dialysis(PD). Duration of hemodialysis was high among subjects with Severe Pulmonary HTN, hence pulmonary HTN should be anticipated early in the course of the disease and should be addressed early. Because the long-term prognosis and mortality in these patients are directly proportional to the severity of pulmonary

hypertension. Hence switch to alternate mode of dialysis, like Peritoneal dialysis should be thought upon.

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