A Tertiary Care Hospital based Study on the Prevalence of Pulmonary Hypertention in Patients with Glomerular Filtration Rate less than 30 Ml /Min Per 1.73 Meter Square on Dialysis

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ABSTRACT

Introduction: Pulmonary artery hypertension (PAH) which can be primary or secondary, has been found to be associated with chronic kidney disease, especially end stage renal disease. Finding prevalence of pulmonary hypertension in early stages of chronic kidney disease is important because it creates very high burden of cardio vascular morbidity and mortality. In this study we have assessed various factors associated with prevalence of pulmonary hypertension in patients with glomerular filtration rate less than 30ml/min per 1.73 meter square on dialysis.

Material and methods: This is a one year, hospital based, prospective observational study of patients aged more than 18 years with GFR less than 30 ml/min per 1.73-meter square on dialysis, who were found to have pulmonary hypertension on echocardiography. The prevalence of pulmonary hypertension in this group of patients and the risk factors in CKD associated with it are calculated followed by a descriptive analysis and interpretation of the data.

Results: The various factors we analyzed and p value for association of pulmonary hypertension in CKD for the percentage of male and female in our study group is 0.241, for distribution of the pulmonary hypertension among different age groups is 0.503, for the significance of diabetic mellitus is 0.595,for systemic hypertension is 0.206, for arterial venous fistula is 0.780,for superimposed infections 0.166, for volume overload is 0.560, for anemia is 0.780, for left ventricular diastolic dysfunction is 0.662, for creatinine clearance is 0.717,for duration of dialysis is 0.000. With above results, only association with significant p-value (0.000) in our study population with pulmonary hypertensions longer duration.

Conclusion: Prevalence of pulmonary hypertension in our study is 22%. The risk factors like age,sex, diabetes, systemic hypertension, AVF, superimposed infection, volume overload, anaemia, LVDD has no influence on pulmonary hypertension in our study, only strong association that we have in our study population with pulmonary hypertension with CKD is longer duration of dialysis.

Keywords: Pulmonary Hypertension (PH), CKD

INTRODUCTION

Though, there has been fast advancement in the medical field which helps in the early and accurate diagnosis of health status of a patient, pulmonary hypertension remains a hidden problem that takes plenty of time in diagnosis from the presence of first symptom. Many patients are diagnosed only in advanced stage of disease.[1] Normal pressure in pulmonary artery is 25/10 mmHg and if the pulmonary artery pressure exceeds 40/20 mmHg or average pressure exceeds 25 mmHg, then the pulmonary hypertension is said to be present.Though the cut off value varies in many studies. If the pressure in the pulmonary artery remains persistently high then the right ventricle of the heart may get hypertrophied,so right ventricle will not be able to pump properly and the symptoms of right heart failure will occur. Pulmonary artery pressure is increased by many conditions and so pulmonary hypertension is classified accordingly. Prevalence of pulmonary artery hypertension inWHO's class1 which is caused mainly by connective tissue disorder, drug, and toxic agents is 15 cases/million adult population.[2,3] Prevalence of idiopathic pulmonary artery hypertension is 5.9 cases/million adult population.[4] Pulmonary hypertension due to systemic sclerosis, portal hypertension, congenital heart disease, and sleep apnea is 7-12%[5,6], 2-16%,[7] 30%[8], and 15-20%[9] respectively. Up to 60%of the patients with severe left ventricular systolic dysfunction and 70% of those with the heart failure with preserved ejection fraction may present with pulmonary hypertension. Almost all the patients with mitral valve diseases have pulmonary hypertension and 65% of those with symptomatic aortic stenosis also will have pulmonary hypertension.[10,11] Chronic thrombo-embolic pulmonary hypertension (CTEPH) prevalence was 3.2 cases/million/year and incidents were 0.9 cases/million/year. A large survey that is conducted in united states that registered information from all form of pulmonary hypertension from 1980-2002 documented that death rate in patients with pulmonary hypertension during these times were stable and ranging from 5.2-5.4deaths/1,00,000.[12,13,14,15]

Chronic kidney disease(CKD) is the global health burden with high economic cost to health system and is an

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independent risk factor for coronary vascular disease. All stages of CKD are associated with increased risk of cardio vascular premature mortality, morbidity and decreased quality of life.

Pulmonary artery hypertension in renal disease is an on-going research topic since it has very limited data. Prevalence of pulmonary hypertension in patients on hemodialysis, peritoneal dialysis and in stage - 5 CKD, ranges from 18.8 - 68.8%, 0.4-2% and 9-39% respectively. No proper epidemiological data are available yet for early stages of CKD. Pulmonary hypertension has direct association with mortality in end stage renal disease. Pulmonary hypertension in end stage renal disease is associated with the worst outcomes.[16-22] It is important to prevent pulmonary hypertension in patient with ESRD in early stages where even kidney transplantation may not reverse the condition,it alsohas high risk of mortality.

Study aimed to find the prevalence of pulmonary hypertension in patients with glomerular filtration rate less than 30ml/min per 1.73-meter square on dialysis in tertiary care hospital, to find the percentage of male and female in our study group and to find the significance of their association with pulmonary hypertension, to find the distribution of the pulmonary hypertension among different age groups and to find the significance of association pulmonary hypertension with diabetic mellitus, systemic hypertension, arterial venous fistula, superposed infection, volume overload, anaemia, left ventricular diastolic dysfunction, creatinine clearance, and duration of dialysis.

MATERIALS AND METHODS

In this prospective observational study conducted during the period of August 2016 to August 2017, we included total of 50 patients who were admitted in hospital fulfilling inclusion criteria. A proforma was made which included the detailed history, clinical examinations, and requisite investigations. After taking informed consent from each patient, detailed history was obtained and complete examination was done. Investigations like complete hemogram, routine urine analysis, blood sugar, serum electrolyte, serum creatinine, blood urea, thyroid function test, liver function test, ultrasound abdomen and pelvis, retroviral serology, hepatitis B and C serology, chest X-ray, echocardiogram, and electrocardiogram were done. GFR is calculated with the help of Cockcroft-Gault formula. Finally, the prevalence of pulmonary hypertension and the risk factors association with it were calculated and statistical analysis was done with the available data.

Inclusion criteria

-Age more than 18years

-Patients with GFR less than 30 ml/minper 1.73-meter square on haemodialysis

Exclusion criteria

Patients who has ejection fraction less than 45%

Patients who are known case of chronic lung disease, thrombo-embolic disease, sarcoidosis, sickle cell disease, HIV, connective tissue disorder, sleep disordered breathing, portal hypertension, congenital heart disease.

STATISTICAL ANALYSIS

The data collected from the patients is tabulated using Microsoft Excel. The chi square test was used to assess the difference in categorical variables between groups. Variables were presented as frequencies (numbers) and proportions (%) and Chi square test was used to compare frequencies. Results were presented in tables with an explanatory paragraph for each table by using Microsoft Office word software version 2010. Level of significance (P value) was considered at 0.05 as cut-off point for significant association.

RESULTS

Distribution of PH in various Age Groups

As seen in table -1, out of the total of number of 50 patients those belonging to age groups less than 40 years, 41-50 years, 51-60years,61-70 years and above 70 years were 6(12%), 7(14%), 24(48%), 9 (18%) and 4(8%) respectively. Patients who were found to have PH in these age groups were 3(50%), 0(0%), 6(25%), 1(11.1%), 1(25%) respectively. So,

Age (in years)	Pulmonary hypertension		Total	P value
	Yes	No		
<=40	3(50%)	3(50%)	6(100%)	0.241
41-50	0(0%)	7(100%)	7(100%)	
51-60	6(25%)	18(75%)	24(100%)	
61-70	1(11.1%)	8(88.9)%	9(100%)	
>70yr	1(25%)	3(75%)	4(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-1: Distribution of PH in various age groups

Sex	Pulmonary hypertension		Total	P Value
	Yes	No		
Male	5(17.9%)	23(82.1%)	28(100%)	0.503
Female	6(27.3%)	16(72.2%)	22(100%)	
Total	11(22.0%)	39(78%%)	50(100%)	

Table-2: Sex distribution of pulmonary hypertension

	Pulmonary HTN			
DM	Yes	No	Total	P value
Yes	7(22.6%)	24(77.4%)	31(100%	0.595
No	4(21.1%)	15(78.9%)	19(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-3: Association of Diabetes with pulmonary hypertension

		Pulmonary hypertension			p value
		Yes	No	Total	
Systemic hypertension	Yes	9(19.6%)	37(80.4%)	46(100%)	0.206
	No	2(50.0%)	2(50%)	4(100%)	
	Total	11(22.0%)	39(78.0%)	50(100%)	

Table-4: Distributionof systemic hypertension in pulmonary hypertension

	Pulmonary HTN			p-value
	Yes	No	Total	
AVF Yes	11(22.4%)	38(77.6%)	49(100%)	0.780
No	0 (0%)	1(100%)	1(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-5: Arteriovenous fistula in CKD and pulmonary hypertension

	Pulmonary htn			P value
	Yes	No	Total	
Superimposed infection				
yes	7(33.3%)	14(66.7%)	21(100%)	0.166
No	4(13.8%)	25(86.2%)	29(100%)	
Total	11(22.0%)	39(78.0%)	50(100%)	

Table-6: Superimposed infection and pulmonary hypertension

	Pulmonary HTN			P value
	Yes	No	Total	
Volume overload				
Yes	6(23.1%)	20(76.9%)	26(100.0%)	0.560
No	5(20.8%)	19(79.2%)	24(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-7: Association of volume overload with pulmonary hypertension

	Pulmonary HTN			P value
	Yes	No	Total	
Anaemia				
Yes	11(22.4%)	38(77.6%)	49(100%)	0.780
No	0(0%)	1(100%)	1(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-8: Anaemia with pulmonary hypertension

	Pulmonary HTN			P value
	Yes	No	Total	
LVDD				
Yes	10(24.4%)	31(75.6%)	41(100%)	0.662
No	1(11.1%)	8(88.9%)	9(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-9: LVDD (with EF>45%) and pulmonary hypertension

	Pulmonary htn			P value
Creatine clearence in GFR in ml	Yes	No	Total	
0-5	1(16.7%)	5(83.3%)	6(100%)	0.717
5-10	7(21.2%)	26(78.8%)	33(100%)	
10-15	3(33.3%)	6(66.7%)	9(100%)	
15-20	0(0%)	2(100%)	2(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-10: Creatinine clearance and pulmonary hypertension

maximum number of patients with PH were in the age group 51-50 and less than 40 years but the p-value was 0.241 which

	Pulmonary htn			P value
Duration of dialysis	Yes	No	Total	
0-5 years	0 (0%)	15 (100%)	15 (100%)	0.000
5-10 years	6 (20.0%)	24 (80.0%)	30 (100%)	
10-15 years	5(100.0%)	0(0%)	5(100%)	
15-20 years	11(22.0%)	39(78.0%)	50(100%)	
Total	11(22%)	39(78%)	50(100%)	

Table-11: Duration of Dialysis and pulmonary Hypertension

was not significant.

In the table 2 we compared the PH distribution among male and female population, in which males 5(17.9%) patients are found to have pulmonary hypertension and among females 6 (27.3%) patients had pulmonary hypertension. There were no significant association of pulmonary hypertension among male and female, since the p value was 0.503.

In the table 3 we analysed significance of association of diabetic mellitus with pulmonary hypertension. In total of 50 patients, 31(62%) patients were found to have DM, and among them 7(22.6%) patients were found to have PH. P value was 0.595, hence there was no significance of DM association with PH.

In the table 4 we analysed significance of association of systemic hypertension with pulmonary hypertension. In total of 50 patients, 46(92%) patients were found to have SHTN, and among them 9(19.6%) patients were found to have PH. P value was 0.206, hence there was no significance of SHTN association with PH.

In the table 5 we analysed significance of association of AVF with pulmonary hypertension. In total of 50 patients, 49(98%) patients were on AVF and one patient was on peritoneal dialysis, and among patients on arteriovenous fistula 11(22.4%) patients were found to have PH, and patient with peritoneal dialysis had no PH and P value was 0.780,which is not significance of AVF association with PH.

In the table 6 we analysed significance of association of super imposed infection with pulmonary hypertension. In total of 50 patients, 21(42%) patients were found to have super imposed infection, and among them 7(33.3%) patients were found to have PH. P value was 0.166, which also no significance of super imposed infection association with PH.

In the table 7 we analysed significance of association of volume overload with pulmonary hypertension. In total of 50 patients, 26(52%) patients were found to have volume overload, and among them 6(23.1%) patients were found to have PH. P value was 0.560, hence there was no significance of volume overload association with PH.

In the table 8 we analysed significance of association of anaemia with pulmonary hypertension. In total of 50 patients, 49(98%) patients were found to have anaemia, and among them 11(22.4%) patients were found to have PH. P value was 0.780, hence there was no significance of anaemia association with PH.

In the table 9 we analysed significance of association of LVDD with pulmonary hypertension. In total of 50 patients,

41(82%) patients were found to have LVDD, and among them 10(24.4%) patients were found to have PH. P value was 0.662, hence there was no significance of LVDD association with PH.

In the table 10 we analysed the pulmonary hypertension distribution and significance of association among the patients with varying range of creatinine clearance. In our study group 6(12%), 33(66%), 9(18%), 2(4%) patients were found to have creatinine clearance between 0-5%, 5-10%, 10-15%, 15-30% respectively and among them pulmonary hypertension was found in 1(16.7%), 7(21.2%), 3(33.3%), 0(0%) respectively. P value is 0.717 insignificant.

In the table 11 we analysed significance of association of duration of dialysis with pulmonary hypertension. In total of 50 patients, 15(30%), 30(60%), 5(10%), 15(30%) patients were found to be between 0-5, 5-10,10-15 years of dialysis respectively, and among them 0(0%), 6(20%), 5(100%), 11(22%) patients were found to have PH respectively. P value was 0.00, hence association of duration of dialysis with pulmonary hypertension is statistically significant.

DISCUSSION

There is no availability of epidemiological data in many developing countries including India for cause of pulmonary hypertension, but in India most common causes of PH are due to rheumatic heart disease, obstructive airway disease and congenital heart disease unlike western countries where idiopathic pulmonary artery hypertension and PH due to right heart disease are common.

Craddock et al say that exposure of dialysis membrane to blood leads to activation of neutrophils which leads to sequestration of neutrophils in the lungs. This phenomenon, is more common if cellulose membranes are used and it causes worsening of lung disease in HD patients.[23]

Presence of connective tissue disease, super imposed infections, haematological and liver diseases can cause pulmonary hypertension in patients with CKD. These conditions cause PH mainly by affecting micro vascular tone in lungs. Endothelial dysfunction has association with pulmonary hypertension in patients with CKD on HD, Main mechanism behind that includes imbalance between vasoconstrictors and vasodilators and high endothelin-1 and low nitric oxide levels affect vascular tone leading to PH.[24,25,26]

The prevalence of PH in CKD in our study was 22%, and the maximum affected age group was 51-60 years.In the study by Qian Zhang et al[27], the total prevalence of PH in CKD was 47.38% with the maximum number of patients seen in age 46.44(±14.63) years. Similarly another study from Iraq[28], showed maximum patients in 50 to 60 years and 60 to 70 years age group (35.3% in both groups).Male and female patients had prevalence of 55.32% and 44.68% respectively and their total number of patients compared to ours was large (n=705) while we had male and female prevalence of 17.95 and 27.3% respectively.

As noted by Qian Zhang et al[27], multivariate odds ratio(with 95%CI) for prevalence of PH in CKD showed that gender, diabetes, systemic hypertension had no significant correlation with PH while eGFR was contributing significantly to it. But, in our study all these parameters were insignificant for PH. Similarly, Ali Abdul Majid Dyab Allawi et al[28] and Thenappan T[29] also found no association between PH in CKD and hypertension even though hypertension is an established risk factor in for PH. Chronic volume overload leads to increased venous return in CKD patients may induce PH but as such we did not get any association between them. Severe anaemia is a well-known cardiovascular risk factor in CKD patients as low haemoglobin leads to hypoxic injury in tissues including pulmonary vasculature.[30] In our study we found no significant association of PH with anaemia while In a retrospective study low haemoglobin had significant impact on PH(P-value-0.000).[27]

In our study, we did not find a correlation between Left ventricular diastolic dysfunction and PH although LV end - diastolic pressure is taken as gold standard for its definition. Measuring LVDD in cases where pulmonary systolic pressure may not be estimated may help in predicting a relation with PH.[31]

According to Yigla M et al, pulmonary hypertension (PH) is a progressive, fatal pulmonary circulatory disease that accompanies many conditions (including left to right side shunt) with compensatory elevated cardiac output. PH also complicates chronic haemodialysis (HD) therapy immediately after the creation of an arteriovenous (AV) access, even before starting HD therapy. It tends to regress after temporary AV access closure and after successful kidney transplantation. This syndrome is associated with a statistically significant survival disadvantage. The laboratory hallmark of this syndrome is reduced basal and stimulatory nitric oxide (NO) levels. It appears that patients with end-stage renal disease (ESRD) acquire endothelial dysfunction that reduces the ability of their pulmonary vessels to accommodate the AV access-mediated elevated cardiac output, exacerbating the PH.[32]

We found 22.4% patients with AV fistula who had PH but this was not significant(p-value>0.780) while flow dependent significance of AV fistula was seen by Magdy M Emara et al.[33] In our study we have not measured AVF flow rate so could not assess its significance.

Comparing our study with Domenici et al[34], who noticed PH in 58.9% cases on HD and 22.2% on PD, we found 22.2% patients on HD having PH but no PH in patient on PD. Similarly another study by Yigla et al[35], found PH 39.7% in patients on HD but none on PD. An study in Iran, based on echocardiographic evaluations, found PH in 30-40% patients on chronic dialysis.[36]

Duration of dialysis significantly added to the development of PH which is evident from our study. This is well supported by Magdy et al[33], who reported duration of dialysis to be quite significantly associated with PH(P-value<0.001 and Pearson correlation 0.780).

Compared with previous studies, risk factors like age, sex, diabetes, systemic hypertension, AVF, superimposed infection, volume overload, anaemia, LVDD are not

associated with pulmonary hypertension in our study. But we found that the longer the duration of dialysis, the higher the possibility of pulmonary hypertension.

Limitations

A larger population based study may provide better data and correlations of above mentioned risk factors.

We have excluded secondary causes of PH in those who are known cases of chronic illness from available information only but have not investigated completely.

CONCLUSION

Prevalence of pulmonary hypertension in our study is 22 percentages. The risk factors like age, sex, diabetes, systemic hypertension, AVF, superimposed infection, volume overload, anaemia, LVDD has no influence on PH in our study. only association that we have in our study population in patients with PH is longer duration of dialysis.

ABBREVIATIONS

PH - Pulmonary hypertension, CKD - Chronic kidney disease, AVF - Arteriovenous fistula, LVDD - Left ventricular diastolic dysfunction, EF - Ejection fraction, ESRD - End stage renal disease, HD - Haemodialysis, PD - Peritoneal dialysis, GFR - Glomerular filtration rate, DM - Diabetes mellitus, SHTN - Systemic hypertension

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