A Hospital Based Study of Pulmonary Arterial Hypertension in Various Stages of Chronic Kidney Disease and Associated Risk Factors among Patients Attending a Tertiary Care Hospital in Ujjain, Madhya Pradesh

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ABSTRACT

BACKGROUND

Multiple mechanisms have been identified contributing to pulmonary arterial hypertension (PAH) in chronic kidney disease (CKD) patients and it is one of the important sequelae of CKD and needs early detection. We wanted to study PAH in various stages of CKD and its association with renal and cardiovascular parameters.

METHODS

This was an observational study. PAH was diagnosed if mean pulmonary artery pressure (MPAP) was ≥ 25 mmHg using 2D - Doppler echocardiography in 96 CKD patients. Staging of CKD was done as per Kidney Disease Improving Global Outcomes (KDIGO) stages 1 - 5. Age, gender, diabetes, hypertension, stages of CKD, corticomedullary differentiation (CMD), estimated glomerular filtration rate (EGFR), urinary albumin creatinine ratio (UACR), left ventricular ejection fraction (LVEF) and left ventricular hypertrophy (LVH) were included as risk factors. Data was analysed by calculating percentage, mean, standard deviation, chi square and t test. P value < 0.05 was taken as statistically significant.

RESULTS

PAH was detected in 37 (38.5 %) of CKD patients. Prevalence of PAH increased with stages of CKD being highest (59 %) in stage 5 and this was found to be statistically significant (P = 0.04). PAH was detected earliest in stage 2 (23.5 %). Lower mean eGFR ml / min / 1.733m^2 (24.43 ± 17.8 vs 40.98 ± 25.7, P = 0.001) altered corticomedullary differentiation (50.9 % vs 20.5 % p = 0.003), reduced LVEF (81 % vs 26.7 % P = 0.000) and LVH (65 % vs 19.6 %, P = 0.000) were significantly associated with PAH in CKD patients.

CONCLUSIONS

PAH in CKD patients increases with CKD stages. Onset of PAH in CKD patients may be earlier and significantly associated with left ventricular dysfunction.

KEYWORDS

Pulmonary Arterial Hypertension, Chronic Kidney Disease, Left Ventricular Ejection Fraction, Left Ventricular Hypertrophy

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BACKGROUND

Pulmonary arterial hypertension is a hemodynamic condition having multiple complex aetiologies and it is associated with high mortality rate. According to the WHO clinical classification of pulmonary hypertension, group 1 includes pulmonary arterial hypertension (PAH) which may be idiopathic, heritable, drug induced, connective tissue disorders, HIV, portal hypertension, group 2 due to left heart disease, group 3 due to lung diseases, group 4 consists of chronic thromboembolic pulmonary hypertension and group 5 includes miscellaneous conditions and end stage renal diseases are included as miscellaneous causes in the classification.[1] Regardless of the aetiology the morbidity and mortality for long standing PAH exceed that expected from the causative condition.[2]

Evidence suggest that PAH is a common co morbidity with the chronic kidney disease (CKD) especially end stage renal disease,[3-7] and rapidly rising burden of chronic kidney disease is a serious concern because most of the cases are detected when irreversible renal damage has occurred. Multiple mechanisms have been identified contributing to pulmonary hypertension in CKD patients including hormonal and metabolic derangements in CKD may lead to pulmonary arterial vasoconstriction and increased pulmonary vascular resistance and PAH may get aggravated in CKD patients due to volume overload, arteriovenous fistula, endothelial dysfunction and severe anaemia. Since both the conditions remain asymptomatic in earlier stages data showing association of PAH in earlier stages 1-3 is scarce.[1,2,7,8] Prevalence of Pulmonary Arterial hypertension in all stages of CKD and its association with PAH, contributing to mortality needs to be explored.

Objectives

1. To study the distribution of PAH and its association with personal and clinical characteristics of patients and association of PAH with stages of CKD. Patients characteristics like age, gender and comorbidities like diabetes, hypertension also determine development of PAH and these conditions are common risk factors for CKD and PAH, hence under this objective their association with PAH and various stages of CKD were studied.
2. To study association of PAH with renal and cardiovascular parameters. Progressive renal dysfunction leads to metabolic derangements which alters the hemodynamic parameters affecting the cardiovascular system especially pulmonary circulation leading to PAH. Under this objective association of PAH with renal parameters like Cortico Medullary Differentiation (CMD), eGFR and Urinary Albumin Creatinine Ratio (UACR) and cardiovascular parameters like LVEF and LVH were studied.

METHODS

This observational study was conducted among the patients attending the Department of medicine, C.R. Gardi hospital, which is a tertiary care centre and a teaching hospital of R.D. Gardi Medical College Ujjain, M.P. from March 2017 to August 2018, India. Study started as per the protocol after its approval from institutional ethics committee. A sample size of 96 was estimated applying formula $4PQ/L^2$ (P- prevalence, Q- 1-P, L- allowable error) at prevalence of PAH in CKD all stages of 40 % and allowable error of 10 %. Those patients who had signs of kidney damage for more than 3 months such as elevated blood urea, decreased eGFR, supportive evidence of albuminuria like raised Urinary Albumin Creatinine ratio (UACR) and USG findings showing altered corticomedullary differentiation (CMD) were eligible participants. Those who had acute illnesses, severe sepsis, medications likely to cause pulmonary hypertension, patients of chronic lung disease, valvular heart disease were excluded. Informed consent of eligible participants was taken.

Data Collection

Data was collected using a predesigned patient Performa to record personal characteristics (age, sex, occupation, education, socio economic status, chief complaints, and history of present & past illness, medication, hospitalization, followed by findings of general and systemic examination. Every patient underwent routine and relevant investigations including blood urea, creatinine, urine ACR, urine routine and microscopy, USG whole abdomen, chest x ray, blood sugar level, ECG, 2D Echocardiography. Blood urea estimation was done by vitrous BUN slide method using VITROS chemistry products calibrator kit 1 on VITROS chemistry systems. Serum creatinine estimation was done by VITROS CREA slides. USG whole abdomen done with GE logiq P6 USING 4c probe, 12 lead ECG was taken, detailed echocardiography examination of all the patients was done using GE logiq P6 machine with 3.5 MHz transducer probe. Kidney Disease Improving Global Outcomes (KDIGO)-Staging of CKD was done as stage 1 (Kidney damage with normal or EGFR levels > 90 ml / min / 1.73 m^2), stage 2 (kidney damage with EGFR levels 60 - 89ml / min / 1.73 m^2), stage 3 (EGFR levels 30 – 59 / min / 1.73 m^2), stage 4 (EGFR levels 15 – 29 / min / 1.73 m^2) & stage 5(kidney failure - EGFR levels < 15 ml / min / 1.73m^2).[9] Measurement of estimated glomerular filtration rate (EGFR) carried out by applying equation from modification of diet in renal disease study (MDRD) - Estimated GFR (ml / min / 1.73m^2) = 175 x $(SCr)^{-1.154}$ x $(age)^{-0.203}$x 1.212 (for blacks)

Multiply by 0.742 for women.[10] Pulmonary arterial systolic pressure (PASP) was calculated using simplified Bernoulli equation (PASP = $4V^2$ + RAP), where RAP is right atrial pressure and v is velocity of the tricuspid regurgitant jet in m / sec, PASP is in mm hg,[11] and mean pulmonary arterial pressure (MPAP) calculated by Chemla formula (MPAP = 0.61PASP + 2 mm Hg).[12] PAH was diagnosed if MPAP was ≥ 25 mm hg.

Statistical Analysis

Quantitative variables analysed by calculating mean with standard deviation, qualitative variables analysed with calculating percentage, P value of < 0.05 was considered for statistical significance applying test of significance (t test or chi square test).

RESULTS

Out of the total 96 study participants, majority 57 (59.4 %) were males of age group 35 - 60 years 65 (67.7 %). Mean age of the study participants was 55.2 ± 10.43 years. Hypertension was present in 51 (53.1 %), and diabetes was present in 36 (37.5 %). Maximum patients were in stage 3 of CKD 30 (31.2 %), 51 (53.1 %) patients were in stages (CKD stages 1,2,3,) and 45 (46.9 %) were in advanced stages (CKD stages 4 & 5).

Pulmonary arterial hypertension (PAH) was found in 37 (38.5 %) patients of CKD. Out of 37 patients with PAH, 22 (59.1 %) were in CKD stage 5, 11 (47.8 %) were in CKD stage 4, 9 (30 %) were in CKD stage 3, 4 (23.5 %) were in CKD stage 2 and none in the stage 1. Prevalence of PAH increased with CKD stages and was found significantly associated (x^2 = 9.809, P = 0.044). Pulmonary hypertension was more among age group > 60 years. 15 (48.4 %) as compared to lower age group 22 (33.8 %), females17 (43.6 %) as compared to males 20 (35.1 %), hypertensive 20 (39.2 %) as compared to non-hypertensive 17(37.8 %), diabetics 15 (41.7 %) as compared to non-diabetics 22 (36.7 %). No significant association was found with age (x^2 = 1.874, P = 0.171), gender (x^2 = 0.707, P = 0.401), hypertension (x^2 = 0.021, P=0.885) and diabetes (x^2 = 0.237, P = 0.626) (Table 1).

Associated Factors N/ %	PAH-Absent N/ %	PAH-Present N	X^2	P Value
Age 35 - 60 years 65(67.7)	43 (66.2)	22 (33.8)	1.874	0.171
Age > 60 years 31(32.3)	16 (51.6)	15 (48.4)		
Gender - male 57(59.4)	37 (64.9)	20 (35.1)	0.707	0.401
Gender - female 39 (40.6)	22 (56.4)	17 (43.6)		
Non Hypertensive 45 (46.9)	28 (62.2)	17 (37.8)	0.021	0.885
Hypertensive 51 (53.1)	31 (60.8)	20 (39.2)		
Non Diabetic 60 (62.5)	38 (63.3)	22 (36.7)	0.237	0.626
Diabetic 36 (37.5)	21 (58.3)	15 (41.7)		
CKD stages 1 04 (4.2)	04 (100.0)	00 (00.0)	9.809	0.044*
CKD stage 2 17 (17.7)	13 (76.5)	04 (23.5)		
CKD stage 3 30 (31.2)	21 (70.0)	09 (30.0)		
CKD stage 4 23 (24.0)	12 (52.2)	11 (47.8)		
CKD stage 5 22 (22.9)	9 (40.9)	13 (59.1)		
Total 96 (100)	**59 (61.5)**	**37 (38.5)**		

Table 1. PAH in CKD Patients and Associated Factors

*- statistically significant P<0.05

Table 2 comparing pulmonary hypertension in early stages 1 - 3 and advanced stages 4 & 5 (Table 2) shows significantly higher prevalence in stages 4 & 5 as compared to stages 1 -3 (53.3 % vs 25.5 % x^2 = 7.824, P = 0.005).

As shown in Table 3 corticomedullary differentiation (CMD) was altered in 57 (59.4 %) of CKD patients and out of this 29 (50.9 %) had PAH and this association was statistically significant (x^2 = 9.013, P = 0.003). Mean EGFR among PAH patients was 24.43 ± 17.8 and 40.98 ± 25.7 among those without PAH and this difference in mean EGFR was statistically significant (t = 3.430, P = 0.001). Higher number of CKD patients with EGFR level < 60ml / min were detected among PAH as compared to EGFR level > 60 among those not having PAH (44 % vs 19 %) and was found statistically significant (x^2 = 4.312, P = 0.038). Left ventricular ejection fraction (LVEF) was significantly lower among PAH patients as compared to those without PAH (81 % VS 26.7 % x^2 = 20.411, P = 0.000). Left ventricular hypertrophy (LVH) was detected in significantly higher proportion among PAH (65 % vs 19.6 %, x^2 = 20.26, P = 0.000). Out of the total 37 patients with PAH majority 30 (81.08 %) had mild to moderate PAH. Severe PAH was present only in CKD stage 4 & 5.

CKD Stage N %	PAH Absent N %	PAH Present N %	X^2	P
stages 1 - 3 51 (53.1)	38 (74.5)	13 (25.5)	7.824	0.005*
stages 4&5 45 (46.9)	21 (46.7)	24 (53.3)		
Total 96 (100)	**59 (61.5)**	**37 (38.5)**		

Table 2. Comparison of PAH in Early (1 - 3) and Advanced Stages (4 & 5) of CKD

*- statistically significant P < 0.05

Parameters	PAH-Absent	PAH-Present	X^2	P Value
CMD - maintained 39 (40.6)	31 (79.5)	8 (20.5)	9.013	0.003*
CMD - altered 57 (59.4)	28 (49.1)	29 (50.9)		
GFR < 60ml / min 75 (78.1)	42 (56.0)	33 (44.0)	4.312	0.038*
GFR > 60ml / min 21 (21.9)	17 (81.0)	4 (19.0)		
ACR < 300 15 (15.6)	9 (60.0)	6 (40.0)	0.016	0.899
ACR>300 81 (84.4)	59 (61.7)	31 (38.3)		
LVEF < 50 21 (21.9)	4 (19.0)	17 (81.0)	20.411	0.000*
LVEF > 50 75 (78.1)	55 (73.3)	20 (26.7)		
LVH - Present 40 (41.7)	14 (35.0)	26 (65.0)	20.26	0.000*
LVH - absent 56 (58.3)	45 (80.4)	11 (19.6)		
Total 96 (100.0)	**59 (100.0)**	**37 (100.0)**		

Table 3. Renal & Cardiovascular Parameters Associated with PAH

* Statistically significant P<0.05

DISCUSSION

Rapidly rising burden of chronic kidney diseases posing challenges in terms of diagnosis, treatment and prevention of complications leading to mortality. Pulmonary arterial hypertension has been identified as one of the important sequel of chronic kidney disease causing untimely deaths and needs to be detected as early as possible. Evidences proved its strong association with End Stage Renal Disease (ESRD) but studies on its association with earlier stages (1-3) of chronic kidney diseases is identified as gap.[8]

Prevalence of PAH in all stages of CKD was 38.5 %, using 2 D Doppler echocardiography. This study found significantly higher prevalence of PAH in CKD stages 4&5 as compared to stages 1 - 3 (53.3 % vs 25.5 % x^2 = 7.824, p = 0.005). Prevalence of pulmonary hypertension in CKD patients is variable in different studies with different inclusion / exclusion criteria, diagnostic criteria and analysis. A study by O' Leary et al. has reported very high prevalence of 68 % among CKD patients with stage 3 or more using right heart catheterization.[13] A meta-analysis including twenty-one observational studies showed pooled prevalence of 32 % in CKD patients without dialysis.[14] Another study used PASP and higher TRV as echocardiographic measures of PH reported 21 % of CKD patients with PAH.[6] Studies from India reported 30 % - 60 % of prevalence of PH in CKD patients.[15,16,17]

The present study found higher prevalence of PAH among higher age group, female gender, hypertensive, diabetes patients but were not significantly associated with PAH. A study by Amin M et al. has reported significantly higher (P = 0.01) prevalence of PH among females,[18] and study by Mehta K.S. et al. reported significantly higher prevalence in males (P = 0.03).[17] Some studies have shown significant association of PAH with diabetes.[5,17] Diabetic nephropathy has been reported as the commonest cause of CKD in a study by Agarwal SK et al.[19] and a study on pulmonary hypertension in patients with ESRD by Yigla M et al. reported diabetes mellitus, arterial hypertension and glomerulopathy as the common aetiologies of renal failure.[7] Diabetic nephropathy being an underlying condition is likely to be associated with PAH in CKD patients. There are studies reporting no significant association of diabetes and PAH.[15,20,21]

There are evidences reporting association of pulmonary hypertension and systemic hypertension.[17,21] Diabetes and hypertension were not found significantly associated with PAH in CKD patients in this study but altered corticomedullary differentiation was found significantly associated with PAH in CKD patients (P = 0.003) indicating glomerulopathy. In the present study out of total 96 patients 41 % had Left ventricular hypertrophy and 21 % had reduced left ventricular ejection fraction. 81 % patients with reduced ejection fraction had PAH, while 65 % of having LVH had PAH. PAH was found strongly associated with left ventricular hypertrophy (P = 0.000) as well as reduced left ventricular ejection fraction (P = 0.000). All those who had both reduced LVEF and LVH 15 (100 %) all had PAH. 10 out of these, had CKD stage 4 &5. This indicates that PAH in CKD patients in this study was visibly due to cardiovascular mechanisms including left ventricular systolic and diastolic dysfunction. Reque J et al. reported significant association of PAH with systolic dysfunction (P = 0.007), diastolic dysfunction (P = 0.01) and volume overload as the most important factor (P = 0.001).[20] Zeng Y et al. in their study on risk factors for pulmonary hypertension have found significant association with reduced ejection fraction in PH group (P = 0.002).[21] As reported earlier most cases of PAH in CKD patients are classified as WHO class II including left heart dysfunction.[8,22]

Present study found significantly higher prevalence of PAH with increasing CKD stages (P = 0.044). Similar findings have been reported by many studies.[16,17,20] This study found that PAH appeared even in early CKD stage 2 it is suggested that all renal disease patients should undergo evaluation of pulmonary pressures as some underlying co morbidities might aggravate hemodynamic changes leading to earlier onset of PAH. Chronic kidney diseases and pulmonary hypertension both have multiple complex aetiologies and risk factors. Some of the risk factors are shared commonly by both,[3] and when both the conditions co-exist it is possible that underlying morbidities independently cause them or chronic kidney disease through various mechanisms causing or aggravating pulmonary hypertension. Onset of pulmonary hypertension in early CKD stages 1 - 3 is required to be explained for improving prognosis. As learned from available evidences pulmonary hypertension once established, worsens the prognosis and adds to the high mortality.[5-8] It is recommended that early detection and prevention of underlying risk factors for pulmonary hypertension is essential in CKD patients. Some limitations were identified in this study such as the present study was hospital based study on small sample; true prevalence estimation was not possible. As no follow up examination was performed hence prognosis in PAH and non PAH patients not reported in this study. Since Right heart catheterization (RHC) remains the gold standard for measurement of pulmonary arterial pressure and this study measured it by echocardiography is an added limitation. Pulmonary Capillary Wedge Pressure (PCWP) could not be measured.

CONCLUSIONS

CKD patients may develop PAH at early stage and its prevalence increases with the severity of CKD. Renal dysfunction leads to hemodynamic changes which causes left ventricular dysfunction and pulmonary hypertension. Both the conditions share risk factors and are multifactorial especially PAH is associated with poor prognosis. Since prevention of PAH is lifesaving, it is important to evaluate CKD patients for hemodynamic changes leading to pulmonary hypertension and also for other causes of PAH.

Limitations

The present study was a hospital based study with a small sample; true prevalence estimation was not possible. As no follow up examination was performed prognosis in PAH and non PAH patients was not reported in this study. Since Right heart catheterization (RHC) remains the gold standard for measurement of pulmonary arterial pressure and this study measured it by echocardiography is an added limitation. Pulmonary Capillary Wedge Pressure (PCWP) could not be measured.

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