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Original Research Article

A Retrospective Study of Clinical Profile and Risk Factors of Pulmonary Arterial Hypertension in Chronic Kidney Disease

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Abstract

Aim: The aim of the present study was to assess the occurrence of pulmonary arterial hypertension in chronic kidney disease and to study the risk factors for development of pulmonary arterial in these patients.

Methods: This was an observational cross section study conducted on 100 patients of CKD (based on KDIGO 2012 criteria) attending medicine OPD or admitted to Department of General Medicine, Jannayak Karpoori Thakur Medical College and Hospital Madhepura,, Bihar, India

Results: Pulmonary hypertension was found in 60 patients (60%) of the study population. No significant association was seen between age, BMI, presence of diabetes and S. Uric acid with presence of PH. Significant association was seen of systolic and diastolic blood pressure with PH. Significant association was also seen of severity of CKD with PH. Presence of hemodialysis and dialysis duration were significantly associated with PH. Of 60 patients with PH, 23 patients had mild PH, 32 patients had moderate PH and 5 patients had severe PH.

Conclusion: We concluded that pulmonary arterial hypertension is significantly associated in patients of CKD and increase in severity of PAH occurs with deterioration of renal function in CKD cases. Anemia, duration of dialysis, hypertension, hyperparathyroidism, AV fistula, increased calcium phosphate product and left ventricular failure are risk factors for development of PAH.

Keywords: Pulmonary arterial hypertension, Chronic kidney disease, risk factors

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Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (PAP) 425 mm Hg as measured by right heart catheterization. PH may be secondary to an underlying cardiac or pulmonary process or may result de novo when an intrinsic pulmonary arteriopathy occurs. Regardless of the mechanism, prolonged elevation in PAP leads to right ventricular dysfunction and consequent morbidity and mortality. [1–7] PH has recently been recognized as a common complication of chronic kidney disease (CKD) and end-stage renal disease (ESRD). To understand this association, it is important to review the hemodynamic determinants of PH and to delineate the spectrum of disorders causing PH.

In common clinical practice, PAP is estimated by echocardiography using the modified Bernoulli equation: PAP = 4 X(tricuspid systolic jet velocity)2 + estimated right atrial pressure, typically measured by vena cava diameter or added based on an assumed, fixed value. [8,9] The limitations of echocardiography in firmly diagnosing PH are well established and include inaccuracies in estimating pulmonary pressure when the tricuspid jet is minimal or difficult to visualize and the reliance on indirect or assumed measurements of right atrial pressure. [10]

Nevertheless, routine reliance on echocardiography to define PH by proxy estimates is driven by a number of factors including cost-effectiveness, the safety of noninvasive measurements, ease of use as a screening tool, and the wider availability of echocardiography compared with right heart catheterization. Despite these advantages, the importance of right heart catheterization in investigating PH in patients with kidney disease cannot be overemphasized. PH is a multifactorial process in ESRD/CKD, and echocardiography is limited in its ability to define the particular contribution of cardiac output (CO), pulmonary capillary wedge pressure (PCWP), and PVR to the elevated PAP. [11] Pulmonary hypertension (PH) is

primarily a disease of the small arteries of the pulmonary vasculature, with progressive obliteration leading to the increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP) that characterize the disease. [12] The increased PVR often leads to right ventricular failure associated with high mortality. [13]

The aim of the present study was to assess the occurrence of pulmonary arterial hypertension in chronic kidney disease and to study the risk factors for development of pulmonary arterial in these patients.

Materials and Methods

This was an observational cross section study conducted on 100 patients of CKD (based on KDIGO 2012 criteria) attending medicine OPD or admitted to Department of General Medicine, Jannayak Karpoori Thakur Medical College and Hospital Madhepura,, Bihar, India for one year. Each patient was subjected to detailed history and clinical examination and relevant investigations were done including CBC, KFT, random blood sugar, S. Electrolytes, S. Calcium, S. Phosphate, S. I PTH, S. uric acid, urine routine and microscopy, USG abdomen, Chest X-Ray, ECG and echocardiography. PAH was diagnosed on the basis of echocardiography with mean pulmonary arterial pressure (MPAP) of ≥25mmHg at rest was taken as diagnostic of pulmonary arterial hypertension. Pulmonary hypertension was classified as:

- Mild (25-40 mHg)
- Moderate (40-60 mmHg)
- Severe (>60 mmHg)

Inclusion Criteria

1. Patients of CKD in stage IV and stage V.

2. Age ≥18 years.

Exclusion Criteria

• Valvular heart disease

• Congenital heart diseases

• Chronic obstructive pulmonary disease

• Chronic parenchymal lung disease

• HIV-infected patients

• Chronic liver disease

• Connective tissue diseases

• Hypothyroidism and hyperthyroidism.

• Pregnancy

• Chronic thromboembolic disorders.

Statistical Analysis

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

Table 1: Characteristics of patients with and without PH

Parameters	With PH (n=60)	Without PH (n=40)	P value
Age	33.27 ± 8.42	35.45 ± 8.62	0.260
BMI	22.58 ± 1.64	23.7 ± 1.61	0.316
SBP	144.6 ± 13.67	139.31 ± 12.12	<0.0001
DBP	85.65 ± 7.47	83.57 ± 6.34	0.0005
CKD stage 4	20	32	<0.0001
CKD stage 5	40	8	<0.0001
Presence of hemodialysis	48	22	0.0004
Hemodialysis duration (weeks)	10.12 ± 4.42	6.44 ± 3.47	0.0001
Presence of AVF	40	0	0.006
Presence of diabetes	25	20	0.325
Hemoglobin	7.43 ± 0.63	8.42 ± 0.48	<0.0001
S. Uric Acid	7.16 ± 0.75	7.08 ± 1.08	0.626

Pulmonary hypertension was found in 60 patients (60%) of the study population. No significant association was seen between age, BMI, presence of diabetes and S. Uric acid with presence of PH. Significant association was seen of systolic and diastolic blood pressure with PH. Significant association was also seen of severity of CKD with PH. Presence of hemodialysis and dialysis duration were significantly associated with PH. Significant association was seen with presence of AVF and presence of PH. Low hemoglobin was also significantly associated with PH. Low serum calcium, high serum phosphate, increased calcium phosphate product and increased intact parathormone were also significantly associated with presence of PH. Patients with PH had lower LVEF%.

Table 2: Characteristics of patients with mild, moderate and severe PH

Parameters	Mild PH (n=23)	Moderate PH (n=32)	Severe PH (n=5)	P value
Age	33.57 ± 10	30 ± 6.44	42.48 ± 2.08	0.001
BMI	23.47 ± 1.52	24.48 ± 1.36	23.57 ± 3.14	0.010
SBP	144.06 ± 12.28	148.32 ± 8.52	146.4 ± 20.32	0.004
DBP	85.75 ± 7.03	86.34 ± 7.3	88 ± 8.56	0.232
CKD stage 4	16	4	0	<0.0001
CKD stage 5	6	28	5	<0.0001
Presence of Hemodialysis	12	27	5	0.068
Hemodialysis duration (weeks)	6.44 ± 1.74	13.47 ± 5.35	18.2 ± 1.88	<0.0001
Presence of AVF	0	14	6	0.001
Presence of Diabetes	6	2	4	0.0003
Hemoglobin	7.53 ± 0.32	7.24 ± 0.52	6.84 ± 0.3	<0.0001
S. Uric Acid	7.12 ± 1.02	6.74 ± 0.89	8.22 ± 0.62	0.071
S. Calcium	7.8 ± 0.52	7.30 ± 0.38	7.35 ± 0.72	0.077
S. Phosphate	6.84 ± 0.54	7.03 ± 0.2	7.18 ± 0.12	<0.0001
Calcium Phosphate Product	49.31 ± 3.4	51.59 ± 2.87	54.46 ± 4.20	<0.0001
iPTH	348.62 ± 54.46	426.74 ± 44.76	459.5 ± 9.31	<0.0001
LVEF%	38.32 ± 4.26	34.56 ± 6.04	36 ± 7.07	0.001

Of 60 patients with PH, 23 patients had mild PH, 32 patients had moderate PH and 5 patients (8.34%) had severe PH. High systolic blood pressure was found to be significantly associated with increased severity of PH. Also as the CKD stage increased, severity of PH also increased significantly. Patients with increased duration of dialysis and patients with AVF had increased severity of PH. Low hemoglobin, increased serum phosphate, increased calcium phosphate product and increased intact parathormone were also found to be significantly associated with increased severity of PH. Also patients with low LVEF% had higher severity of PH.

Table 3: Multivariate logistic regression to find out independent significant risk factor of pulmonary hypertension

Factors	p-value	Odds ratio
Systolic blood pressure (mmHg)	0.655	0.945
Diastolic blood pressure (mmHg)	0.632	1.058
Dialysis duration (weeks)	0.380	0.860
Hemoglobin (gm/dL)	0.450	0.326
S. Calcium (mg/dL)	0.135	0.000
S. Phosphate (mg/dL)	0.159	0.000
Calcium Phosphate product	0.132	8.246
Intact parathormone (pg./mL)	0.418	1.009
LVEF%	0.644	0.958
CKD stage		
4		1
5	0.447	4.763

On performing multivariate logistic regression after adjusting for confounding factors, none of the factors was found to be an independent significant risk factor for pulmonary hypertension.

Discussion

Cardiovascular disease is the most common cause of morbidity and mortality in patients with chronic kidney disease (CKD). [14] The focus is usually on left ventricular failure causing increased morbidity and mortality in the patients of CKD whereas pulmonary arterial hypertension (PAH) is an overlooked cardiovascular complication of CKD, especially in end-stage renal disease (ESRD). Elevated pulmonary arterial pressure (PAP) can be observed secondary to heart, lung, or systemic disorders. PAH is defined as "a mean pulmonary artery pressure more than or equal to 25 mmHg at rest or 30 mmHg at exercise." [15] Navaneethan et al. reported an increased mortality in a cohort of PH patients with CKD, [16] but did not investigate a population of CKD patients for the presence of PH. The hemodynamic profiles of PH (pre-capillary PH versus post-capillary PH) in the CKD population have not been fully explored. Therefore, studies employing invasive hemodynamics are needed to

gain insight into the etiology of PH among CKD patients. Moreover, prior studies have lacked information about important co-morbidities and echo variables that may influence the relationship between PH and CKD.

Pulmonary hypertension was found in 60 patients (60%) of the study population. No significant association was seen between age, BMI, presence of diabetes and S. Uric acid with presence of PH. Significant association was seen of systolic and diastolic blood pressure with PH. Significant association was also seen of severity of CKD with PH. Presence of hemodialysis and dialysis duration were significantly associated with PH. Significant association was seen with presence of AVF and presence of PH. Low hemoglobin was also significantly associated with PH. Low serum calcium, high serum phosphate, increased calcium phosphate product and increased intact parathormone were also significantly associated with presence of PH. Patients with PH had lower LVEF%. Similar results were observed by Zhang et al [17] where patients with higher BMI had severe PH. However in a study by K. Rama Subbu et al [18] patients with more severe PH had lower BMI. Although, obesity is risk factor for the development of cardiovascular disease, diabetes mellitus, hypertension, renal disease and metabolic abnormalities, the results of association of BMI with severity of PH are conflicting.

Of 60 patients with PH, 23 patients had mild PH, 32 patients had moderate PH and 5 patients had severe PH. High systolic blood pressure was found to be significantly associated with increased severity of PH. Also as the CKD stage increased, severity of PH also increased significantly. Patients with increased duration of dialysis and patients with AVF had increased severity of PH. Low hemoglobin, increased serum phosphate, increased calcium phosphate product and increased intact parathormone were also found to be significantly associated with increased severity of PH. Also patients with low LVEF% had higher severity of PH. In studies by Zhang et al[17] and K. Rama Subbu et al[18] no significant association was seen in either systolic blood pressure or diastolic blood pressure with severity of PH. Hence, although hypertension is associated with the presence of PH in CKD patients in most of the previous studies, no definitive association was seen with the severity of PH. On performing multivariate logistic regression after adjusting for confounding factors, none of the factors was found to be an independent significant risk factor for pulmonary hypertension. Our study also showed a significant association of increased phosphate, increased calcium phosphate product and increased iPTH with the severity of PH. In contrast, Zhang et al [17] in their study showed no such association between calcium, phosphate and calcium phosphate values with severity of PH, however they noticed that Ipth values in severe PH was much higher compared to mild and moderate PH.

In dialysis patients, the prevalence of PH was much higher, which had some specific risk factors for PH. In this study, patients with congenital heart failure and acute heart failure before had been excluded. However subclinical heart failure was common in ESRD patients. The causes might include hypertension, salt and water overload, pleotropic effects of uraemic toxins and myocardial ischemia. These factors were more prevalent in patients with PH. Arteriovenous fistulae (AVF) are considered the gold standard for HD access. [19] They result in increased venous return with a concomitant increase in cardiac output and also lead to decreased systemic vascular resistances. [20] In a study of patients receiving PD, LV mass index, alongside low serum albumin and fluid overload, was a predictor of PH in a multivariate model. [21]

Conclusion

We concluded that pulmonary arterial hypertension is significantly associated in patients of CKD and increase in severity of PAH occurs with deterioration of renal function in CKD cases. Anemia, duration of dialysis, hypertension, hyperparathyroidism, AV fistula, increased calcium phosphate product and left ventricular failure are risk factors for development of PAH. Treatment of these risk factors can decrease the progress and severity of PAH, thereby decreasing the morbidity and mortality in CKD.

References

1. Rubin LJ. Pathology and pathophysiology of primary pulmonary hypertension. The American journal of cardiology. 1995 Jan 19; 75(3):51A-4A.
2. Yigla M, Fruchter O, Aharonson D, Yanay N, Reisner SA, Lewin M, Nakhoul F. Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients. Kidney international. 2009 May 1;75(9):969-75.
3. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, Orringer EP. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. British journal of haematology. 2006 Jul;134(1):109-1 5.
4. Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Internal medicine journal. 2007 Jul;37(7):485-94.
5. Dallari R, Barozzi G, Pinelli G, Merighi V, Grandi P, Manzotti M, Tartoni PL. Predictors of survival in subjects with chronic obstructive pulmonary disease treated with long-term

oxygen therapy. Respiration. 1994 Jan 20;61 (1):8-13.
6. Rosenkranz S. Pulmonary hypertension: current diagnosis and treatment. Clinical Research in Cardiology. 2007 Aug;96:527-41.
7. Badesch DB, Champion HC, Gomez Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. Journal of the American College of Cardiology. 2009 Jun 30; 54(1_Supplement_S):S55-66.
8. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. Journal of the American College of Cardiology. 1985 Aug 1;6(2):359-65.
9. Sicari R, Gargani L, Wiecek A, Covic A, Goldsmith D, Suleymanlar G, Parati G, Ortiz A, Massy Z, Martinez-Castelao A, Lindholm B. The use of echocardiography in observational clinical trials: the EURECA-m registry. Nephrology Dialysis Transplantation. 2013 Jan 1;28(1):19-23.
10. Fisher MR, Forfia PR, Chamera E, Housten-Harris T, Champion HC, Girgis RE, Corretti MC, Hassoun PM. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. American journal of respiratory and critical care medicine. 2009 Apr 1;179(7):615-21.
11. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ. A report of the american college of cardiology foundation task force on expert consensus documents and the american heart association. Circulation. 2009 Apr 28;119(16): 2250-94.
12. Vonk-Noordegraaf A, Souza R. Cardiac magnetic resonance imaging: what can it add to our knowledge of the right ventricle in pulmonary arterial hypertension? Am J Cardiol. 2012;110(6 Suppl):25S–31S.
13. Sharma M, Pinnamaneni S, Aronow WS, Jozwik B, Frishman WH. Existing drugs and agents under investigation for pulmonary arterial hypertension. Cardiol Rev. 2014;22(6): 297–305.
14. Clementi A, Virzì GM, Goh CY, Cruz DN, Granata A, Vescovo G, Ronco C. Cardiorenal syndrome type 4: a review. Cardiorenal medicine. 2013;3(1):63-70.
15. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and Diagnosis of Pulmonary Hypertension. J Am Coll Cardiol 2013; 62:42-50.
16. Navaneethan SD, Wehbe E, Heresi GA, Gaur V, Minai OA, Arrigain S, Nally JV, Schold JD, Rahman M, Dweik RA. Presence and outcomes of kidney disease in patients with pulmonary hypertension. Clinical Journal of the American Society of Nephrology. 2014 May 7;9(5):855-63.
17. Zhang Q, Wang L, Zeng H, Lv Y, Huang Y. Epidemiology and risk factors in CKD patients with pulmonary hypertension: a retrospective study. BMC nephrology. 2018 Dec;19:1-8.
18. Ramasubbu K, Deswal A, Herdejurgen C, Aguilar D, Frost AE. A prospective echocardiographic evaluation of pulmonary hypertension in chronic hemodialysis patients in the United States: prevalence and clinical significance. International journal of general medicine. 2010 Oct 5:279-86.
19. Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. American journal of kidney diseases. 2001 Jan 1;37(1): S66-70.
20. Kawar B, Ellam T, Jackson C, Kiely DG. Pulmonary hypertension in renal disease: epidemiology, potential mechanisms and implications. American journal of nephrology. 2013;37(3):281-90.
21. Ünal A, Sipahioglu M, Oguz F, Kaya M, Kucuk H, Tokgoz B, Buyukoglan H, Oymak O, Utas C. Pulmonary hypertension in peritoneal dialysis patients: prevalence and risk factors. Peritoneal dialysis international. 2009 Mar;29(2):191-8.