



ORIGINAL ARTICLE: NEPHROLOGY

Pulmonary Hypertension in Patients of Chronic Kidney Disease on Maintenance Hemodialysis: Study from a Tertiary Care Center in Central India

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Abstract

To study the incidence of pulmonary hypertension (PH) in chronic kidney disease (CKD) stage V patients on maintenance hemodialysis (HD) at our center. To compare clinical and metabolic variables among CKD patients with and without PH to search for possible etiologic factors. Comparison of PH in CKD patients at baseline and after 3 months of sildenafil therapy. The study was conducted in the Department of Nephrology, Sri Aurobindo Institute of Medical Sciences, Indore, for a period of 1 year from December 2021 to November 2022. All CKD patients on maintenance HD at our center were included in the study. A pre-structured proforma was used to record patient data. Detailed clinical examination, 2DECHO, and Biochemical tests were done. All patients with mean pulmonary artery pressure (mPAP) > 25 mmHg on 2D echocardiography were considered to have PH and were started on sildenafil therapy 20 mg three times a day for 3 months. PH was classified as mild PH (mPAP > 25 up to 40 mmHg), moderate PH (mPAP > 40 mmHg to 60 mmHg), and severe PH (mPAP > 60 mmHg). Patients were then followed for 3 months to look for episodes of dyspnea and emergency admissions and reassessed after 3 months by repeat 2D echocardiography to find improvement in PH. A total of 102 patients were analyzed during the study period; among them, 40 patients (39.2%) had PH. Out of them, 18 patients (45%) had mild PH, 14 patients (35%) had moderate PH, and 8 patients (20%) patients had severe PH. Average age of our patients was 48.8 ± 9.4 years, the majority being men. On comparing the clinical features between patients with and without PH, none of the clinical parameters had any statistically significant impact on PH. Also, none of the laboratory parameters had statistical significance among PH and non-PH groups. Among the patients with PH, 25 patients (62.5%) had Arteriovenous (AV) fistula, 10 patients (25%) had temporary dialysis catheters. Eight patients (20%) had jugular catheters, two patients (5%) had femoral catheters, and 5 (12.5%) patients had tunneled jugular catheters. Initially, 102 patients were enrolled in the study. Of these, 40 (39.2%) had PH and 62 (60.7%) did not. Patients who had PH started sildenafil 20 mg three times a day. Of these 40 patients, at 3 months, eight patients were lost to follow-up, and 32 patients with PH remained in the study. The mean PH at baseline was 47.8 ± 8.9 mmHg and at 3 months the mean PH was 44.4 ± 7.8 mmHg. mPAP at baseline and at 3 months was compared with the severity of PH. After 3 months, there were 14 patients with mild PH, 11 patients with moderate PH, and 7 patients with severe PH. After treatment, five patients downgraded from mild to no PH, four patients from moderate to mild PH, and three patients from severe to moderate PH. Emergency admissions in each group of PH declined after 3 months, and the result was statistically significant. Echocardiographic findings were compared in patients with PH and without PH, but the difference in patients on HD with PH and without PH was not statistically significant. PH is a significant problem in CKD patients on HD. This issue needs to be evaluated in a timely manner to avoid the risk of morbidity and mortality. It is vital to treat them at the earliest to prevent life-threatening complications.

Keywords: chronic kidney disease; hemodialysis; mean pulmonary artery pressure; pulmonary hypertension; two-dimensional echocardiography

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Introduction

Pulmonary hypertension (PH) is an elevation of pulmonary arterial pressure, which can be due to heart, lung, or systemic disorders. Pulmonary artery pressure (PAP) is defined as a sustained elevation of PAP ≥ 25 mmHg at rest or ≥ 30 mmHg with exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of ≥ 15 mmHg (1). PH may be secondary to an underlying cardiac or pulmonary process or may result due to intrinsic pulmonary arteriopathy. Prolonged elevation of PAP leads to right ventricular dysfunction and consequent morbidity and mortality (2). PH is exceedingly prevalent in both pre-dialysis and dialysis-dependent populations but is often overlooked and underestimated. Endothelial dysfunction and remodeling of the medial and intimal layers of the pulmonary vasculature characterize PH, resulting in constrictive and occlusive vascular lesion (3). PH is categorized as primary if there is no identifiable cause or secondary if there is an apparent cause or risk factor. The updated clinical classification system of PH has divided cases into five etiologic categories based on etiologic mechanisms (4).

The first etiologic category represents the PH that may be familial, idiopathic secondary [due to congenital systemic-to-pulmonary shunts, portal hypertension, collagen vascular disease, human immunodeficiency virus (HIV) infection, drugs, toxins, etc.] or associated with considerable venous or capillary involvement (pulmonary veno-occlusive disease or pulmonary-capillary hemangiomatosis).

The second etiologic category is due to left heart disease (left-sided atrial or ventricular heart disease and left-sided valvular heart disease).

The third etiologic category, one of the commonest, represents patients with lung disease and/or hypoxemia (Interstitial lung disease or chronic obstructive lung disease, alveolar hypoventilation disorders, sleep-disordered breathing, chronic exposure to high-altitude, or developmental abnormalities).

The fourth category represents the PH due to chronic thrombotic and/or embolic disease [thromboembolic obstruction of proximal or distal pulmonary arteries and nonthrombotic pulmonary embolism (parasites, tumor, or foreign material)].

Finally, the fifth category encompasses miscellaneous disorders such as histiocytosis-X, sarcoidosis, lymphangiomatosis, and chronic kidney disease (CKD) on dialysis.

The prevalence of PH in dialysis patients is substantially high. It varies across different studies from 17 to 49.53% depending on the mode of dialysis and other selection factors, such as the presence of other cardiovascular comorbidities. Oxidative stress and inflammation are highly prevalent in the hemodialysis (HD) population. Increased oxidant activity and decreased antioxidant ability cause excessive oxidative stress, and factors such as malnutrition, chronic volume

overload, and autonomic dysfunction lead to a persistent inflammatory state. Both oxidative stress as well as persistent inflammation eventually causes endothelial dysfunction, which contributes to the development of cardiac dysfunction. However, the role of oxidative stress and inflammation in the development of PH is yet to be fully established (5). In patients with End Stage Kidney Disease (ESKD), there is a high prevalence of comorbidities, particularly cardiac disease, that potentially contribute to the higher-than-usual prevalence of PH in this population. There is a high prevalence of heart failure, connective tissue disease, thromboembolic disease, and pulmonary and sleep disorders in ESRD patients that contribute to the pathogenesis of PH. AV fistula also has been implicated in the development of PH in ESRD patients on HD. The role of AV access flow in the development of PH is considered most likely due to increased vascular flow in the setting of altered cardiovascular physiology or pathology and hormonal and metabolic alterations of ESRD. As an example, the increase in cardiac output following access creation is accompanied by an increase in pulmonary arterial pressure (6, 7). Fluid overload also contributes to the pathogenesis of PH.

Aims and Objectives

1. To study the incidence of PH in CKD stage V patients on maintenance HD at our center.
2. To compare clinical and metabolic variables among CKD patients with and without PH to search for possible etiologic factors.
3. Comparison of PH in CKD patients at baseline and after 3 months of sildenafil therapy.

Material and Methods

The study was conducted in the Department of Nephrology, Sri Aurobindo Institute of Medical Sciences, Indore, for a period of 1 year, from December 2021 to November 2022.

Inclusion criteria

All CKD stage 5 patients are on maintenance HD at our center. Age more than 18 years.

Exclusion criteria

Pregnancy

Patient already on medication for PH. Informed written consent was taken from all the patients.

A pre-structured proforma was used to record patient data. Detailed clinical examination, 2DECHO, and biochemical tests were done. 2D ECHO was done post-HD for all patients.

All patients with mean pulmonary artery pressure (mPAP) > 25 mmHg on 2D echocardiography were considered to have PH and were started on sildenafil therapy 20 mg three times a day for 3 months. PH was classified as mild PH (mPAP > 25 up to 40 mmHg), moderate PH (mPAP > 40 up to 60 mmHg), and severe PH (mPAP > 60 mmHg).

Patients on sildenafil therapy were followed for 3 months to look for episodes of dyspnea and emergency admissions and reassessed after 3 months by repeat 2D echocardiography to see improvement in PH.

Statistics

Statistical tests (t-test and Chi-square test) were used to analyze the data by using the statistical package SPSS version 22. A P-value < 0.05 was considered statistically significant.

Results

A total of 102 patients were analyzed during the study period. Of these, 40 patients (39.2%) had PH—18 patients (45%) had mild PH, 14 patients (35%) had moderate PH, and eight patients (20%) patients had severe PH as depicted in Figure 1. Average age of our patients was 48.8 ± 9.4 years, with the majority being men. On comparing the clinical features between patients with and without PH, none of the clinical parameters had any statistically significant impact on PH as shown in Table 1. Also, none of the laboratory parameters

had statistical significance among PH and non-PH groups as shown in Table 2.

Among the patients with PH, 25 patients (62.5%) had AV fistula, 10 patients (25%) had temporary dialysis catheters—eight patients (20%) jugular and two patients (5%) femoral, and five patients (12.5%) had tunneled jugular catheters as shown in Figure 2.

PH was more common in patients with AV fistula.

Initially, 102 patients were enrolled in the study. Of these, 40 patients (39.2%) had PH and 62 patients (60.7%) did not. Patients who had PH started sildenafil 20 mg three times a day. At 3 months, of these 40 patients, eight patients were lost to follow-up, and 32 patients with PH remained in the study. The mean PH at baseline was 47.8 ± 8.9 mmHg, and at 3 months, the mean PH was 44.4 ± 7.8 mmHg. Mean PAP at baseline and at 3 months was compared with the severity of PH.

The mPAP in each group of PH declined. However, the result was not statistically significant. After 3 months, there were 14 patients with mild PH, 11 patients with moderate PH, and seven patients with severe PH. After treatment, five patients downgraded from mild to no PH, four patients from moderate to mild PH, and three patients from severe to moderate PH as shown in Table 3.

Episodes of dyspnea leading to emergency admissions were compared in PH groups at baseline and after 3 months.

Emergency admissions in each group of PH declined after 3 months and the result was statistically significant as shown in Table 4.

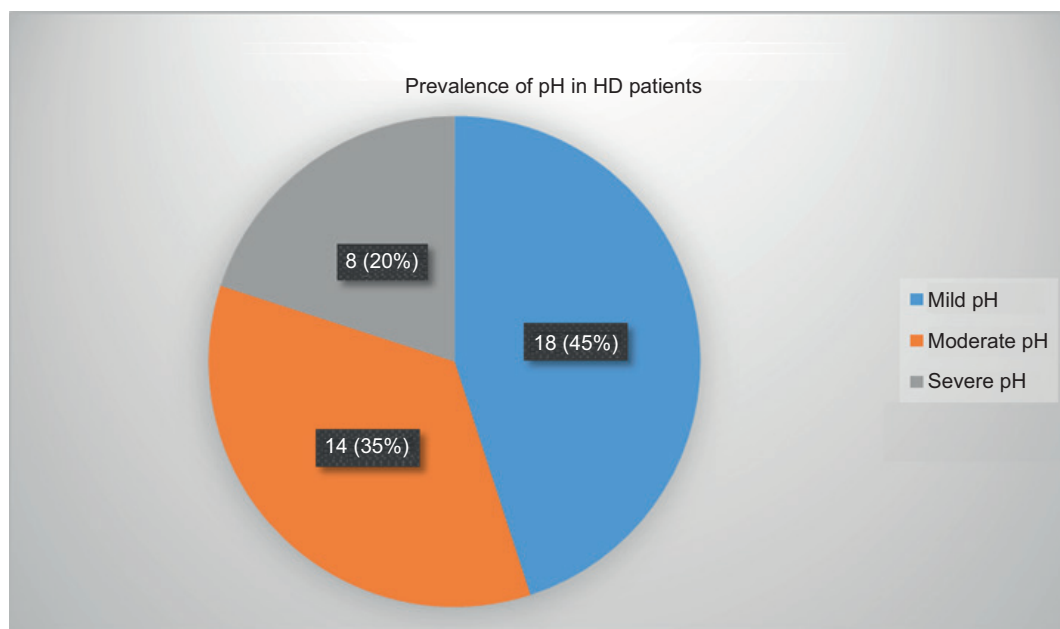


Figure 1: Prevalence of PH in HD patients. PH, pulmonary hypertension; HD, Hemodialysis.

Table 1: Comparison of clinical characteristics between patients with PH and without PH.

Characteristics	With PH	Without PH	P
Age	48.8 ± 9.4	47.3 ± 8.2	0.30
Males	24 (60%)	36 (58%)	0.38
Etiology of CKD			
Diabetic kidney disease	12 (30%)	18 (29%)	0.64
Hypertension	6 (15%)	10 (16.1%)	0.71
Chronic glomerulonephritis	8 (20%)	11 (17.7%)	0.71
Chronic interstitial nephritis	5 (12.5%)	9 (14.5%)	0.72
ADPKD	1 (2.5%)	3 (4.8%)	0.76
Unknown	8 (6.25%)	11 (17.7%)	0.71
Hypertension	39 (97.5%)	60 (96.7%)	0.12
Cerebrovascular accident	2 (5%)	3 (4.8%)	0.77
Ischemic heart disease	7 (17.5%)	8 (12.9%)	0.75
Dialysis vintage (in months)	36 ± 4	35 ± 2	0.09

PH, pulmonary hypertension; CKD, chronic kidney disease; ADPKD, Autosomal Dominant Polycystic Kidney Disease.

Table 2: Comparison of laboratory parameters between patients with PH and without PH.

Parameter	With PH	Without PH	P
Hemoglobin (g/l)	9.1 ± 1.2	9.4 ± 1.7	0.32
S. Creatinine (mg/dl)	8.1 ± 2.3	8.9 ± 3.5	0.20
S. Calcium (mg/dl)	8.4 ± 1.1	8.7 ± 0.7	0.09
S. Phosphorous(mg/dl)	4.8 ± 0.8	4.7 ± 0.6	0.47
S. Albumin (g/dl)	3.9 ± 0.4	4.01 ± 0.5	0.24

PH, pulmonary hypertension.

Echocardiographic findings were compared between patients with PH and without PH but the difference was not statistically significant as shown in Table 5.

Discussion

The incidence of PH in HD patients has been reported to be 25–51% in various studies (6, 8, 9). In our study, the incidence of PH in HD patients was 39.2% which was comparable to other studies. We also compared various clinical and laboratory parameters to search for possible etiology of PH. Still,

none of the clinical parameters and etiology of CKD were statistically significant in PH and non-PH groups. In our study, the mean age of HD patients with PH was 48.8 ± 9.4 years, and the majority were males, with no significant effect found between age and gender on the incidence of PH. This was comparable to other studies where there was no significant association between age as well as gender on the incidence of PH (10–13). Also, risk factors like diabetes, hypertension, cerebrovascular accident, and ischemic heart disease had no statistically significant association with incidence of PH in our study like other studies (10, 14). Dialysis vintage has a direct relationship to the development of PH (15). However, in our study, the dialysis vintage was comparable in PH and non-PH groups. None of the laboratory parameters had a statistically significant difference between PH and non-PH groups. AV fistula has been considered a cause of PH in HD patients (16). In our study, also most common vascular access in patients with PH on HD was AV fistula (62.5%). Echocardiographic findings were compared in patients with PH and without PH, but the difference in patients on HD with PH and without PH was not statistically significant. However, in certain studies (10, 17), prevalence of mitral regurgitation was more among patients with PH on HD. In our study, the prevalence of mitral regurgitation was more among patients on HD with PH than without PH but the difference was not statistically significant. Sildenafil, a phosphodiesterase inhibitor, has been implicated in the management of PH via its nitric

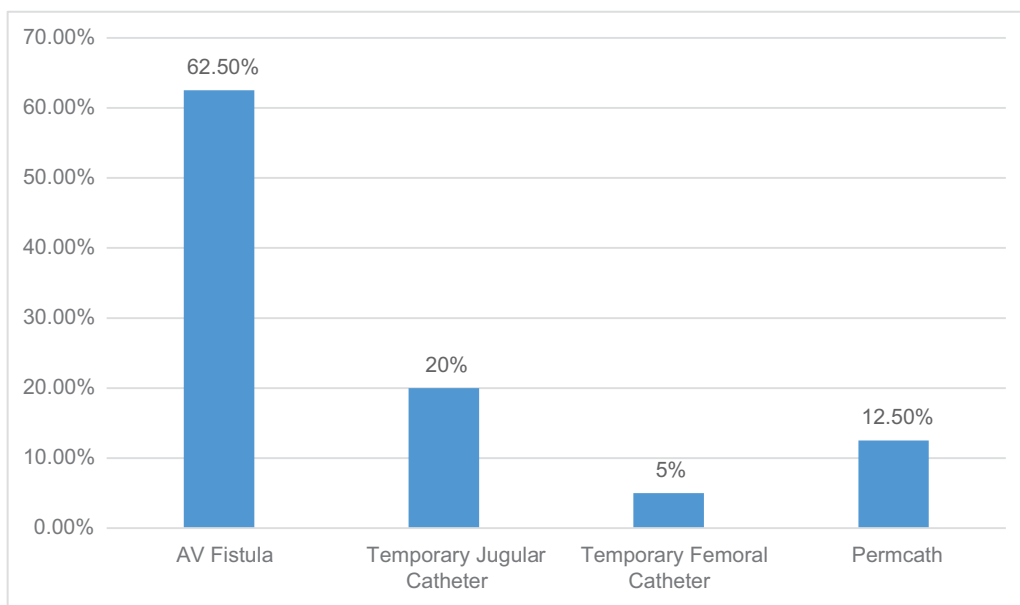


Figure 2: PH in various vascular access. PH, pulmonary hypertension.

Table 3: Severity of PH.

Severity of PH	mPAP (Baseline)	mPAP (At 3 months)	P
Total	47.8 ± 8.9 (n = 40)	44.4 ± 7.8 (n = 32)	0.09
Mild PH	34.7 ± 6.5 (n = 18)	31.6 ± 5.7 (n = 14)	0.16
Moderate PH	50.5 ± 8.2 (n = 14)	46 ± 7 (n = 11)	0.16
Severe PH	72.6 ± 9.1 (n = 8)	67.5 ± 8.4 (n = 7)	0.28

PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure.

Table 4: Emergency admissions pre- and post-treatment.

Severity of PH	Mean episodes of emergency admissions (Baseline)	Mean episodes of emergency admissions (At 3 months)	P
Mild PH	0.5 ± 0.09 (n = 18)	0.38 ± 0.08 (n = 14)	0.0005
Moderate PH	1.14 ± 0.2 (n = 14)	0.8 ± 0.1 (n = 11)	0.0001
Severe PH	1.8 ± 0.4 (n = 8)	1.3 ± 0.3 (n = 7)	0.0181

PH, pulmonary hypertension.

oxide-mediated vasodilation. It improves exercise capacity, WHO functional class, and hemodynamics in patients with symptomatic PH (18). Very few studies have been done on its role for PH in HD patients. There was a reduction in mPAP in all mild, moderate, and severe forms of PH after sildenafil therapy in our study. This can be compared to a study

by Abdelrahman Ali Elbraky et al. (19) where the effect of sildenafil on PAP in PH patients on HD was studied. We compared the mean episodes of emergency admissions due to dyspnoea before and after Sildenafil therapy, which was found to be reduced in all grades of PH and this reduction was found to be statistically significant.

Table 5: Comparison of echocardiographic findings in patients with PH and without PH.

Echocardiographic findings	With PH (n = 40)	Without PH (n = 62)	P
EF (%)	52 ± 5	54 ± 7	0.12
LVH	30 (75%)	44 (70.9%)	0.16
RWMA	14 (35%)	18 (29%)	0.36
MR	25 (62.5%)	26 (41.9%)	0.46
TR	20 (50%)	22 (35.4)	0.43

PH, pulmonary hypertension; EF, Ejection Fraction; LVH, Left Ventricular Hypertrophy; RWMA, Regional Wall Motion Abnormality; MR, Mitral Regurgitation; TR, Tricuspid Regurgitation.

Conclusion

PH is a significant problem in CKD patients on HD. This issue needs to be evaluated in a timely manner to avoid the risk of morbidity and mortality. It is vital to treat them at the earliest to avoid life-threatening complications. Our study confirmed the efficacy of Sildenafil therapy in patients on HD with PH in the form of a decline in mPAP and reduction in episodes of dyspnea and emergency admissions. More research is needed in this area to understand the pathogenesis and therapeutic options further.

Conflicts of Interest

None.

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