Original Article

Pulmonary Hypertension in Various Stages of Chronic Kidney Disease in Indian Patients

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Abstract

The prevalence of pulmonary hypertension (PH) in chronic kidney disease (CKD) in Indian patients has been evaluated in this study. In addition, association of PH with CKD etiology, its prevalence in various CKD stages, correlation between the severity of PH with CKD duration, various related biochemical parameters, and their relation to PH in CKD patients were analyzed. This cross-sectional and prospective study included 200 CKD patients. Detailed history and clinical examination were recorded. Hemoglobin, blood urea nitrogen (BUN), serum creatinine, albumin, and calcium-phosphorus product were recorded. Pulmonary function test was evaluated and two-dimensional echo was done 4 hours post dialysis. The prevalence of PH in CKD patients was 60.5%, with mean pulmonary artery systolic pressure (PASP) of 38.52 ± 7.32 mmHg. The mean age of those with PH was 47.85 ± 13.09 years. PH was more common in males ($p = 0.03$). The prevalence of PH increased as CKD stage advanced ($p < 0.001$). Diabetes and hypertension had a strong association with PH ($p < 0.001$). The prevalence ($p = 0.003$) and severity ($p = 0.011$) of PH increased with increase in CKD duration. In patients on hemodialysis (HD), the prevalence ($p < 0.001$) and severity ($p = 0.022$) of PH was significant compared to those on conservative treatment. The prevalence ($p < 0.001$) and severity ($p < 0.001$) of PH significantly increased as duration of HD increased. The prevalence of PH was significantly higher in patients with arteriovenous fistula ($p = 0.002$). Serum creatinine ($p = 0.02$) and serum calcium-phosphorus product ($p < 0.001$) were significantly higher in patients with PH. The prevalence of PH in CKD patients was 60.5%. There was a positive correlation between PH and duration of CKD, duration of HD, BUN, serum creatinine, and serum calcium-phosphorus product.

Keywords: *Arterio-venous fistula, chronic kidney disease, hemodialysis, pulmonary hypertension*

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem both in terms of the number of patients and the cost of treatment. The severity may have been underestimated as patients with CKD are more likely to die of cardiovascular diseases (CVD) than to reach end-stage renal disease (ESRD).[1] As per the data from the Indian Registry, the most common causes of CKD in India are diabetic nephropathy (30.3%) followed by chronic glomerulonephritis (15.8%) and hypertension (14.8%).[2] Approximately 30% of patients with diabetes mellitus (DM) have diabetic nephropathy, and with the growing number of DM patients and aging population, there is likely a parallel increase in CKD incidence.[1]

CKD leads to many comorbidities that affect patients of all stages of the disease. Kidney function can only be partly replaced by maintenance dialysis.[3] At present out of three modalities of treatment – renal transplant, hemodialysis (HD), and peritoneal dialysis – maximum number of patients are on HD.[4] Recently an association has been found between HD and pulmonary hypertension (PH).[5]

The majority of the patients with CKD have hypertension with diastolic dysfunction, arteriovenous fistulas (AVF), anemia, uremic lung, volume overload with interstitial pulmonary edema, and a high cardiac output state, all of which can lead to increased pulmonary vascular pressures.[6,7] Uremic endothelial dysfunction, disrupting the balance between vasodilators (such as prostacyclins and nitric oxide) and vasoconstrictors (such as endothelin1, plasma asymmetric dimethylarginine

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and thromboxane), contribute further to PH.[8,9] Extraosseous vascular calcification and recurrent pulmonary thromboembolic disease (due to vascular access thrombectomy and microbubbles stemming from HD tubing or dialyzers) are other postulated mechanisms.[10-12]

PH in ESRD is associated with increased mortality rates. In an observational study, patients on haemodialysis with PH had mortality of 30.4% compared to 8.5% without PH.[13] Specific considerations such as prostacyclin analogues and endothelin receptor antagonists can be considered in carefully selected cases.

There is a paucity of data on the incidence and prevalence of PH in CKD among Indian patients. Here, we focus on the clinical epidemiology of PH in patients with CKD at our tertiary care center along with relationship between the prevalence of PH and CKD staging.

Materials and Methods

This was a prospective study done at our tertiary care and teaching hospital, from March 2013 to March 2015, after obtaining permission from Institutional Ethics Committee.

Inclusion criteria

Patients with all the following were included.

1. All CKD stage 2 and above (as per K-DOQI guidelines): (eGFR was calculated using the MDRD formula)
2. Age group >18 years
3. Normal pulmonary function tests on spirometry
4. Written informed consent.

Exclusion criteria

1. All pregnant females and
2. All known cases of PH secondary to left-sided heart diseases (e.g., coronary heart diseases [ruled out by normal ECG along with absence of regional hypokinetic segment and ejection fraction of >55% on two-dimensional (2D) ECHO], rheumatic heart diseases, and valvular heart diseases
3. Systemic disorders that can cause PH such as collagen vascular diseases and HIV infection and pulmonary diseases (COPD, pulmonary embolism, and scleroderma).

All patients underwent a detailed clinical evaluation, and findings were entered in a case record form. Medical history included age, sex, associated comorbidity, particularly diabetes and hypertension, CKD etiology and duration, dialysis and its duration, and presence or absence of AVF. Laboratory investigations like complete blood count, urine routine, blood urea nitrogen (BUN), serum creatinine, serum sodium and potassium, serum calcium and phosphate, serum uric acid, serum bilirubin, serum aspartate aminotransferase and alanine aminotransferase, and serum albumin. ECG and 2D ECHO were done in all patients.

Transthoracic Doppler echocardiography for measurement of pulmonary artery systolic pressure (PASP) based on the tricuspid regurgitation jet[5] was performed on all patients. Those on hemodialysis underwent echocardiography 4 hours post dialysis.

PH was defined when mean pulmonary artery pressure exceeded 30 mmHg.[5] PH was further categorized as mild (>30 to <35 mmHg), moderate (35 to 50 mmHg), and severe (>50 mmHg).

Statistics

At the end of the study period qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi-square test with continuity correction for all 2 × 2 tables and with or without continuity correction in the rest and Fisher's exact test for all 2 × 2 tables where p value of Chi-square test was not valid due to small counts. Quantitative data was represented using mean ± SD and median.

Analysis of quantitative data (CKD stages, blood pressure, pulmonary hypertension grading, etc.) between a qualitative variable with two subgroups was done using unpaired *t*-test. Analysis of quantitative data between qualitative variables with more than two subgroups was done using one-way ANOVA if data passed "Normality test" and by Kruskal-Wallis test if data failed "Normality test," with application of appropriate *post hoc* test.

Results

Out of the total 200 patients included in the study, 121 (60.5%) patients had PH. Majority, 56 (46.28%) of CKD patients showed moderate PASP followed by 48 patients mild group (39.67%) and 17 severe PH (14.05%). There was no effect of age on prevalence of PH. Out of the total 121 patients with PH, 75 (61.98%) were males. PH was more common in males than females and statistically significant ($p = 0.03$). There was statistically significant association between CKD stages and PH ($p < 0.001$). None of the patients in CKD stage II revealed PH, while 12 (9.91%), 26 (21.48%), and 83 (68.59%) patients of CKD stage III, IV, and V, respectively, had PH. Fifty-four out of 63 diabetics (85.71%) had PH whereas 30 out of 52 hypertensives (57.69%) had PH. There was a strong association between diabetes and hypertension with PH ($p < 0.001$) [Table 1].

As seen in the Table 2, PH was noted in 10 out of 24 patients (44.67%) with CKD duration <6 months; in 63 out of 113 patients (55.75%) with CKD duration 6–12 months and in 48 out of 63 patients (76.19%) with CKD duration >12 months. This statistically signifies the strong association between CKD duration and PH ($p = 0.003$); as the duration of CKD increases, the number of PH cases increases [Tables 2 and 3]. Out of 48 patients with mild PASP 14 (29.16%) had CKD for >12 months; out of

Table 1: Pulmonary hypertension (PH) and etiology of CKD

Etiology	PH present (%)	Total	*P*
Diabetes Mellitus (DM)	54 (44.62)	63	<0.001
Hypertension (HTN)	30 (24.79)	52	<0.001
Undetermined (UNDETR)	18 (14.87)	31	0.3694
Obstructive uropathy (OU)	4 (3.30)	17	0.0691
Chr. Glomerulonephritis (CGN)	5 (4.13)	16	0.1336
Other (OTHER)	10 (8.26)	21	0.8273
Chr. tubulointerstitial dis.	4 (3.30)	9	
Polycystic kidney disease	2 (1.65)	5	
Genitourinary TB	2 (1.65)	3	
Reflux disease	1 (0.82)	3	
Ischemic nephropathy	1 (0.82)	1	
Total	121 (100)	200	

Table 2: CKD duration and incidence of pulmonary hypertension

CKD duration (months)	PH absent (*n*)	PH present (*n*)
<6 (*n*=24)	14	10
6-12 (*n*=113)	50	63
>12 (*n*=63)	15	48

Table 3: CKD duration and severity of pulmonary hypertension

PH (mmHg)	CKD duration in months		
	<6	6-12	>12
31-34 (*n*=48)	6	28	14
35-50 (*n*=56)	4	30	22
>50 (*n*=17)	0	5	12

56 patients with moderate PASP, 22 (39.28%) had CKD for >12 months; whereas out of 17 patients with severe PASP, 12 (70.58%) had CKD for >12 months. This again signifies the strong association between duration of CKD and severity of PH ($p = 0.011$) [Table 3].

Treatment modality and pulmonary hypertension

Out of 88 patients on HD, 72 (81.81%) had PH; whereas only 49 (43.75%) out of 112 patients on conservative management had PH. Statistically significant difference between patients treated with HD and those on conservative treatment ($p < 0.001$) was noted.

Out of 48 patients with mild PASP, 24 (50%) were on HD; whereas out of 56 patients with moderate PASP, 33 (58.93%) were on HD; but out of 17 patients with severe PASP, majority i.e., 15 (88.23%) were on HD. This statistically signifies the strong association between HD with severity of PH ($p = 0.022$).

Hemodialysis duration and pulmonary hypertension

As seen in the Table 4, out of 10 patients on HD <6 months, only 2 (20%) developed PH. Of 37 patients on HD between 6–12 months, 31 (83.78%) developed PH while out of 41 patients on HD >12 months, 39 (95.12%) developed PH. Patients with longer duration of HD had higher prevalence of pulmonary hypertension ($p < 0.001$). Out of 39 patients on HD for >12 months, 10 (25.64%) had severe PH; whereas out of 31 patients on HD between 6–12 months only 5 (9.68%) had severe PH. This shows that there is statistically significant association between duration on HD and severity of PH ($p < 0.001$).

Out of 57 patients with AVF, 51 (89.47%) had PH, whereas out of 31 patients who did not have AVF, 21 (67.74%) have PH ($p = 0.002$). Out of 113 anemia patients, 82 (72.57%) had PH ($p > 0.05$); out of 77 patients with BUN >45 mg/dl, 60 (77.92%) had PH ($p > 0.05$); out of 83 patients with serum creatinine >5 mg/dl, 72 (86.74%) had PH ($p < 0.05$); out of 18 patients with serum calcium-phosphorus (Ca × P) product >55 mg^2/dl^2, 15 (83.33%) had PH ($p < 0.001$) [Table 5]. Thus, patients with serum creatinine >5 mg/dl were prone to have PH as well as those with Ca × P >55 mg^2/dl^2. The association of BUN >45 mg/dl and hemoglobin <10 g/dl with PH was not statistically significant.

There was a positive correlation between PH and duration of CKD, duration of dialysis, BUN, serum creatinine, and calcium phosphorous product, whereas a negative correlation was found between hemoglobin and PH [Table 6].

Discussion

PH, a disorder characterized by elevated pulmonary artery pressure, is a progressive disorder complicating heart, lung, or systemic diseases, with increased morbidity and mortality regardless of its etiology.[14] Recently it has been found that PH is a strong independent predictor of morbidity and mortality in HD patients.[15,16] In an observational study of 58 HD patients, with a mean follow-up of 30 months, patients with PH had mortality of 30.4% compared with 8.5% among patients without PH ($p < 0.03$).[17] Yigla *et al.*,[15] in their cohort of CKD patients, reported significantly lower survival than those without PH with 1 year, 3 years, and 5 years survival rates of 78.6% versus 96.5%, 42.9% versus 78.8%, and 25.2% versus 66.4% respectively ($p = 0.0001$). There are very few Indian studies addressing the prevalence of PH in CKD patients. In patients with ESRD, PH has been recognized to be a frequent condition and appears to be independent from cardiovascular disease prevalence.[15]

The prevalence of PH in CKD patients in the present study was 60.5% with mean PASP of 38.52 ± 7.32 mmHg. Tarras *et al.*[18] found PH prevalence to be as low as 26.74% and Moniruzzaman *et al.*[5] found it to be as high as 68.6%. In another Indian study Patel *et al.*[19] studied 100 patients (69 males, 31 females) who were on conservative management, HD or continuous ambulatory

peritoneal dialysis (CAPD). The prevalence of PH in this cohort was 41% and the highest prevalence was in the HD group (33%). The variability in the prevalence of PH among CKD patients in different studies[5,18-21] can be explained by the difference in the ethnicity of the population studied as well as in the study group, regarding stage of CKD, mode of dialysis (HD vs PD), comorbid conditions such as COPD/CHF and inclusion criteria. Though these studies considered different parameters and are not truly comparable, most concluded that there was high prevalence of PH among CKD patients.

Table 4: Duration of Hemodialysis (HD) and Pulmonary hypertension

HD duration (months)	PH absent (%)	PH present (%)	Total
< 6	8 (50)	2 (2.78)	10
6-12	6 (37.5)	31 (43.06)	37
>12	2 (12.5)	39 (54.17)	41
TOTAL	16 (100)	72 (100)	88

p<0.001 (significant)

Table 5: Biochemical variables and pulmonary hypertension

Variables	PH absent (%)	PH present (%)	Total	*P*
Hb <10 gm/dl	31 (27.43)	82 (72.57)	113	0.0823
BUN >45 mg/dl	17 (22.08)	60 (77.92)	77	0.240
Sr. creat >5 mg/dl	11 (13.25)	72 (86.75)	83	0.020
Ca × P product >55 mg^2/dl^2	3 (16.67)	15 (83.33)	18	<0.001

There was no effect of age on prevalence of PH in our study. This result was similar to the study by Mazdeh *et al*.[22] (p = 0.58) and Tarras *et al*.[18] (p = 0.37). Patel *et al*. also did not find correlation between age and PHT (p = 0.402).[19] In the present study PH was more common in males (p = 0.03). Tarras *et al*.[18] (p = 0.69) could not find a significant association between sex and PH among CKD patients. Moniruzzaman *et al*.[5] found a male predominance (male to female ratio of 2:1) in their study.

In the present study, statistically significant association between CKD stages and PH (p < 0.001) was noted, inferring that advanced the CKD stage is, the higher is the incidence of PH. Being a tertiary referral centre, our patients are usually late referrals and all patients in our study group were in stage III, IV, or

Table 6: Correlation between pulmonary hypertension and other dependent variables

	CKD duration	Dialysis month	Hb	BUN	Serum creatinine	Ca × P	Pulmonary hypertension
CKD duration							
Pearson Correlation	1	0.486**	−0.144*	0.159*	0.198**	0.195**	0.227**
Sig. (two-tailed)		0.000	0.041	0.025	0.005	0.006	0.001
n	200	88	200	200	200	200	200
Dialysis month							
Pearson Correlation	0.486**	1	−0.023	0.274**	0.298**	0.324**	0.397**
Sig. (two-tailed)	0.000		0.835	0.010	0.005	0.002	0.000
n	88	88	88	88	88	88	88
Hb							
Pearson Correlation	−0.144*	−0.023	1	−0.293**	−0.368**	-0.084	-0.316**
Sig. (two-tailed)	0.041	0.835		0.000	0.000	0.234	0.000
n	200	88	200	200	200	200	200
BUN							
Pearson Correlation	0.159*	0.274**	−0.293**	1	0.497**	0.138	0.327**
Sig. (two-tailed)	0.025	0.010	0.000		0.000	0.051	0.000
n	200	88	200	200	200	200	200
Serum creatinine							
Pearson Correlation	0.198**	0.298**	-0.368**	0.497**	1	0.203**	0.407**
Sig. (two-tailed)	0.005	0.005	0.000	0.000		0.004	0.000
n	200	88	200	200	200	200	200
Serum CA × P							
Pearson Correlation	0.195**	0.324**	−0.084	0.138	0.203**	1	0.396**
Sig. (two-tailed)	0.006	0.002	0.234	0.051	0.004		0.000
n	200	88	200	200	200	200	200
Pulmonary hypertension							
Pearson correlation	0.227**	0.397**	−0.316**	0.327**	0.407**	0.396**	1
Sig. (two-tailed)	0.001	0.000	0.000	0.000	0.000	0.000	
n	200	88	200	200	200	200	200

**Correlation is significant at the 0.01 level (two-tailed). *Correlation is significant at the 0.05 level (two-tailed)

V. Yang *et al*.[23] found PH prevalence of 23.76% (24/101) in stage II and 48.15% (13/27) in GFR <60 mL/min/1.73 m^2 group ($p < 0.05$) raising the alarm that PH exists and may be prevalent prior to drop in GFR to <60 ml/min/1.73 m^2. Severe PH was detected in CKD patients in stage-V and stage-VD along with increased prevalence of PH and cardiovascular morbidity as renal disease progressed in study by Li *et al*.[24]

The exact mechanisms of PH in higher stages of CKD remain poorly understood. PH might be induced and/or aggravated by left ventricular disorders and risk factors typical of CKD, including volume overload, AVF, sleep disordered breathing, exposure to dialysis membranes, endothelial dysfunction, vascular calcification and stiffening, and severe anemia.[16,25] ESRD-related PH, for the first time, was grouped into the 5th subtype (PH with unclear multifactorial mechanisms) of PH by the World Symposium of PH (WSPH).[26] This group includes PH in CKD without significant cardiac and pulmonary diseases. Ruling out these comorbid conditions—which were found in 40%–70% of patients in most cohorts—typically involves chest radiography, pulmonary function tests, CT scans, and ventilation/perfusion scans.[16]

Significant association was seen between CKD duration and PH prevalence ($p = 0.003$) and and its severity ($p = 0.011$) in our study. Havlucu *et al*.[27] ($p < 0.05$) and Patel *et al*.[19] ($p = 0.002$) found similar association between duration of CKD and PH in their study. The greater the duration of the CKD, the longer will be exposure of the patients to the altered cardiovascular physiology including synergistic effects of increased PVR, increased cardiac output, and elevated PCWP, and hence, the chances of having more severe pulmonary hypertension increases.[16] There was a statistically significant association between diabetes and hypertension with PH ($p < 0.001$) in this study. In a study conducted by Agarwal *et al*.,[28] there was similar statistical association of diabetes ($p = 0.04$) with PH but not of systemic hypertension ($p = 0.2$). However, the study by Fabian *et al*.[29] showed stastically strong association of both diabetes ($p = 0.021$) and hypertension ($p = 0.0074$) with PH. Hypertension and diabetes mellitus, two dominant causes of kidney disease, trigger LV diastolic dysfunction, an alteration bound to increase pulmonary venous and arterial pressure.[30] Chronic volume overload, a factor implicated in LV disorders and in high venous return in patients with CKD, may induce pulmonary venous hypertension by increasing pulmonary blood flow and adversely affecting LV function. In addition, myocardial stiffness secondary to myocardial infarction, another frequent complication of CKD, may contribute to PH. Two echocardiographic studies have shown that CKD patients with PH have significantly higher estimates of left-sided filling pressures, with higher estimates of PCWP and left atrial size, suggesting chronic volume overload.[28,31]

Our cohort showed statistically significant presence of PH in patients treated on HD than treated conservatively ($p < 0.001$). The HD group not only showed higher prevalence of PH but also had more severe PH ($p = 0.022$) than those on conservative treatment. The prevalence of PH among patients on HD was studied by Moniruzzaman *et al*.[5] and Kiykim *et al*.[32] and was found to be 68.6% and 68.8%, respectively. Though, effect of duration of CKD in patients on HD is important in pulmonary hypertension pathogenesis, factors specific to HD like exposure to dialysis membrane, AV fistula contributes to pulmonary hypertension. Uremic patients on chronic HD therapy, via AV access exhibit decreased Nitric oxide production. This endothelial dysfunction, coupled with prolonged elevation of endothelin, reduces capacity of pulmonary circulation to maintain AV access mediated elevation of cardiac output and contributes to pulmonary hypertension.[16,24,25]

Domenici *et al*.[21] who reported that PH was found in 23/39 (58.9%) of the HD patients and 2/9 (22.2%) of the PD patients; PASP was significantly higher in HD patients than in PD patients ($p < 0.01$). Further, Patel *et al*.[19] demonstrated that 41 patients had PH, of whom 33% were on HD. The prevalence and average PASP is lower in PD patients than in HD patients. In our study group, there were no patients in the PD group as none of them fulfilled the inclusion criteria and/or were excluded for one or more reasons as per criteria. Neutrophil activation secondary to blood–dialysis membrane contact accompanied by reversible neutrophil sequestration in the lung also contributes to causing or worsening microvascular lung disease in HD patients.[33]

In the present study, patients with longer duration of HD had higher prevalence of PH. Emara *et al*.[34] ($p < 0.001$) and Patel *et al*.[19] (P = 0.001) also found a similar association. The presence of AVF itself, which is accompanied by commonly occurring anemia and fluid overload, further increases the PH.[35] There was statistically significant association between duration on HD and severity of PH in the present study ($p < 0.001$). There are many studies similar that of Issa *et al*.[36] and Bozbas *et al*.[37] showing association of duration of HD and PH, but none have studied the association between the duration of HD and severity of PH.

In the present study, out of 57 patients with AVF, 51 had PH, whereas, out of 31 patients without AVF, 21 had PH. This shows there was a strong association between AVF and PH ($p = 0.002$). Havlucu *et al*.[27] showed similar association ($p < 0.05$); however, Agarwal *et al*.[28] ($p = 0.1$) did not find a similar association. This difference could have been due to the difference in the AVF duration as well as the population studied. In a case report, PH had reversed after ligation of the patient's large fistula.[38] The AVF created causes decrease in the systemic vascular resistances with increase in venous return and cardiac output, which

helps maintain proper blood flow to all organs and tissues. These adaptations increase pulmonary blood flow and set the stage for PH. Well-performed studies show that pulmonary pressure increases in strict temporal relationship with AVF creation[35] and that PH tends to worsen over time in this population.[27,29]

Various variables were taken into consideration such as hemoglobin levels, BUN, serum creatine, and serum calcium × phosphorus product (Ca × P) out of which only serum creatine and Ca × P product were found to be statistically associated with PH, $p = 0.02$ and $p < 0.001$, respectively. Significant association of hemoglobin, BUN, serum creatine, and serum Ca × P product was observed in various studies.[19,22,27,34] It is postulated that low hemoglobin levels can contribute to PH by aggravating hypoxia.[39] PH in patients having raised Ca × P product may be attributed to increased stiffness of pulmonary vasculature caused by vascular calcification. Increased uremic load reflected by BUN and serum creatinine level causing release of inflammatory markers (acute phase reactive protein and cytokines, including IL-1β, TNF-α and IL-6), especially in HD patients can be a factor for development of PH in these patients.[40] Role of uremic endothelial dysfunction in pulmonary vascular resistance has been highlighted in literature.[16] Increasing duration of CKD with higher stages is an important factor, as these are associated with rising creatinine, worsening secondary hyperparathyroidism with higher CaxPO4 product; though, with, adequate dialysis, these latter two factors should get well controlled. However, inadequate HD, especially in India, due to various factors can result into higher Serum creatinine levels, secondary hyperparathyroidism, raised CaxPO4 product, pulmonary vasculature calcification and stiffness and hence resultant PH.

Limitations of the study

1. The sample size is small
2. The study excluded patients with CKD stage I and II and patients on peritoneal dialysis
3. The diagnosis of PH was based on indirect echocardiographic estimates of PA systolic pressure and not by right heart catheterization, which is the gold standard
4. Significant coronary artery disease was not excluded by coronary angiography and stress test
5. There is no long-term follow-up of patients.

Conclusions

The prevalence of PH in CKD patients is 60.5%. Prevalence of PH had positive correlation with stage of CKD, duration of CKD, those on hemodialysis, and those with AVF. The severity of PH was also directly proportional to the duration of CKD and duration of hemodialysis. Calcium phosphorus product were significantly higher in CKD patients with PH than without it.

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Conflicts of interest

There are no conflicts of interest.

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