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The Incidence and Severity of Pulmonary Hypertension among Patients with Chronic Kidney Disease

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Abstract

Purpose: Chronic kidney disease (CKD) is a major health problem and is closely linked with cardiovascular disease. Pulmonary hypertension (PH) is considered a common comorbidity in CKD patients. This study aimed at assessing the correlation between CKD and pulmonary hypertension.

Methodology: This is a retrospective study that recruited 100 Egyptian patients with stage 3 and above Chronic Kidney Disease (CKD) (KDOQI guidelines). The study sample was composed of 100 patients with 60% overall prevalence of PH. Transthoracic echo Doppler study was performed to measure pulmonary artery systolic pressure based on tricuspid jet in the sample.

Findings: There was significant association between PH and severity of renal disease. The hemodialysed group showed a higher prevalence of PH with a more severe PH compared to groups not on regular dialysis. The study had provided evidence that PH is a common comorbidity in CKD patients and is directly proportional with the stage and duration of CKD.

Recommendations: Pulmonary hypertension should be regularly assessed using echocardiography in CKD patients specially those on regular dialysis.

Keywords: *Pulmonary hypertension, chronic kidney disease, dialysis.*

INTRODUCTION

Chronic kidney disease (CKD) and cardiovascular diseases (CVD) are closely connected which pose a major global public health problem. They have many common primary causes like diabetes mellitus and arterial hypertension. CKD is an independent risk factor for CVD onset. The United States Renal Data System reports that in patients with CKD the prevalence of any CVD is almost doubled, estimated at 69.8% versus 34.8% in the normal population **(1).** It is common that CKD and End Stage Renal Disease patients have Pulmonary Hypertension (PH) as co-morbidity. It usually involves multiple and is complicated by most of the cardiovascular and respiratory diseases **(2-4).** PH is associated with increased hospitalization and mortality risk in CKD patients **(4,5)**

The accurate incidence and prevalence of early to moderate CKD are usually hard to estimate because patients are often asymptomatic. The prevalence of CKD in the general population is around 10% to 14%. Similarly, albuminuria and GFR below 60 ml per min per1.73 mt2 have a prevalence of 7% and 3% to 5%, in order **(6).** There have been several definitions to describe CKD, the best was in 2002 by The Kidney Disease Outcomes Quality Initiative (KDOQI) and the international guideline group Kidney Disease Improving Global Outcomes (KDIGO) subsequently modified these definitions. **(7, 8)** These guidelines have facilitated communication between physicians and helped taking proper interventions at the different stages of the disease.

CKD is defined by (KDOQI) and (KDIGO) as either kidney damage or a reduced glomerular filtration rate (GFR) to below than 60 mL per min per1.73 m2 for a period of 3 months at least. Regardless the cause, the damage to nephrons and reduction of renal mass is usually irreversible and leads to continuous drop in the GFR. **(8)**

The stages of CKD are classified as follows **(9):**

- Stage 1: Kidney damage with normal or elevated GFR (more than 90 mL per min per 1.73 m 2)
- Stage 2: Mild decrease in GFR (range between 60-89 mL per min per 1.73 m 2)
- Stage 3a: Moderate decrease in GFR (range between 45-59 mL per min per 1.73 m 2)
- Stage 3b: Moderate decrease in GFR (range between 30-44 mL per min per 1.73 m 2)
- Stage 4: Severe decrease in GFR (range between 15-29 mL per min per 1.73 m 2)
- Stage 5: Kidney failure (the GFR is below 15 mL per min per 1.73 m 2 or dialysis)

The study aims at assessing the presence of PH in patients with chronic kidney disease as there are very few studies addressing its prevalence among CKD in Egyptian patients.

MATERIALS AND METHODS

This is a retrospective study done at Cairo kidney center, from July 2020 to May 2021.

Inclusion Criteria

The patients included are:

1. Classified as stage 3 and above CKD patients (as per KDOQI guidelines): Modification of Diet in Renal Disease Study (MDRD) formula was used to calculate the eGFR **(10, 11)**
2. Eighteen years of age or older
3. With normal pulmonary function tests.

4. Signed written informed consent.

Exclusion criteria

The excluded patients were:

1. Pregnant females.
2. Secondary PH cases due to either left sided heart diseases, rheumatic or congenital heart diseases.
3. Having systemic disorders such as collagen vascular diseases and connective tissue disease and Primary Lung diseases including (Chronic Obstructive Pulmonary Diseases (COPD), scleroderma, and pulmonary embolism) that might cause PH.

A case record form was formed for all patients containing a detailed clinical evaluation and findings including 1)age, 2) sex, 3)CKD with details on etiology and duration and type of dialysis and the presence or absence of arteriovenous fistula (AVF), 4) associated comorbidity (particularly diabetes and hypertension). It also included laboratory investigations as 1) complete blood count, 2) serum sodium and potassium, 3) serum aspartate aminotransferase, 4) serum albumin, 5) urine analysis , 6) serum calcium , 7) alanine aminotransferase, 8) serum creatinine and blood urea nitrogen (BUN), 9) serum bilirubin, 10) serum uric acid, 11) serum phosphate.

All patients had ECGs done and PHT was measured by transthoracic echocardiography based on tricuspid regurgitation jet **(12).** This was done 4 hours after dialysis sessions in dialysis patients. PH was diagnosed when mean pulmonary artery pressure was found above 30 mmHg. It was further subdivided into a) mild (above 30 and below 35 mmHg), b) moderate (Between 35, and 50 mmHg), and c) severe (Above 50 mmHg) **(12).**

Statistics

After all the data was collected and revised properly, frequency and percentage were used to express the qualitative data. Chi – square test was used with continuity correction for all 2 × 2 tables. It was also used without continuity correction for some data. Fisher's exact test was used to assess the 2× 2 tables where P value of Chi – square was not accepted due to small sample size.

Distribution of the quantitative data was thoroughly assessed. Mean ± SD and median were the best representing measures of the data in the sample. Unpaired t-test was used to analyze the quantitative data between a qualitative variable with two subgroups. This quantitative data included CKD stages, blood pressure levels, pulmonary hypertension grades, etc.) When the quantitative data between qualitative variables had more than two subgroups, one-way ANOVA test was the test used for analysis. This was only after applying the "Normality test" to the data. If the data didn't pass the "Normality test", Kruskal- Wallis test was used for analysis with application of appropriate post hoc test.

RESULTS

About 60 (60%) patients had PH in a total of 100 patients participated in the study. As regards classification of PH in CKD patients, 28 (46.67%) showed moderate PH, 24 patients showed mild PH (40%) and 8 patients showed severe PH (13.33%). Age had no effect on prevalence of PH. 37 (61.67%) of a total of 60 patients were males. There was statistically significant direct correlation between the stages of CKD and PH ($p < 0.001$). In CKD stage III, IV and V 4 (6.67%), 14 (23.33%) and 42 (70%) in row had PH. Twenty seven out of 31 diabetics (84.37%) had PH whereas from

the 26 hypertensive patients (57.69%) 15 had PH. This indicates a strong significant correlation between hypertension and diabetes Mellitus with PH ($p < 0.001$).

In patients with CKD duration <6 months, PH was noted in 5 out of 12 patients (41.67%) whereas it was noted in 31 out of 57 patients (54.38%) with CKD period of 6 months to one year and in 24 from 31 patients (77.41%) with CKD period more than one year. This confirms the statistical association between CKD period and PH ($p = 0.003$) with a directly proportionate relationship between length of the period of CKD and the detected number of PH cases (Tables 1 and 2).

Table 1: Duration of CKD and incidence of pulmonary hypertension

Duration of CKD (in months)	**PH not present (*n*)**	**PH found (*n*)**
Below 6 (*n*=12)	**7**	**5**
6‑12 (*n*=57)	**26**	**31**
Above 12 (*n*=31)	**7**	**24**

From 24 patients with mild PH, 7 (29.16%) had CKD for more than one year; from 27 patients with moderate PH, 11 (39.28%) had CKD for more than one year; whereas from 9 patients with severe PH, 6 (66.67%) had CKD for more than one year. This again marks the significant strong correlation between the length of the period of CKD and severity of PH ($p = 0.011$) (Table 2).

Table 2: Duration of CKD and severity of pulmonary hypertension

	Duration of CKD (in months)		
PH (mmHg)	**<6**	**6-12**	**>12**
31‑34 (*n*=24)	**3**	**14**	**7**
35‑50 (*n*=27)	**2**	**14**	**11**
>50 (*n*=9)	**0**	**3**	**6**

In patients on regular Hemodialysis (HD) total patients was 44, 36 (81.81%) had PH. whereas only 25 (44.64%) from the 56 patients on conservative management had PH. It was noted that there is a statistically significant difference between patients on regular HD and patients treated conservatively ($p < 0.001$). From 24 patients with mild PH, 12 (50%) were on HD; whereas from 28 patients with moderate PH, 16 (57.14%) were on HD; but from 8 patients with severe PH, the vast majority i.e., 8 (100%) were on HD. This statistically shows how significant is the association between the severity of PH and HD ($p = 0.022$).

As illustrated in the Table 3, only 1 (25%) from 4 patients on HD <6 months developed PH. Of the 19 patients on HD for a period of 6–12 months, 16 (84.21%) developed PH while from the 21 patients on HD more than 12 months, 19 (91%) developed PH. There was higher prevalence of pulmonary hypertension in patients with longer duration of HD.($p < 0.001$). Out of 21 patients on HD for more than 12 months, 6 (28.6%) had severe PH; whereas from 19 patients on HD for a period of 6–12 months only 3 (15.8%) had severe PH. This confirms the statistically significant direct correlation between severity of PH and the duration of HD ($p < 0.001$)(tables 2 and 3).

Table 3: Duration of Hemodialysis (HD) and pulmonary hypertension

HD period (months)	PH not present (%)	PH found (%)	Total
<6	3 (75)	1 (25)	4
6-12	3 (16)	16 (84)	19
>12	2 (9)	19 (91)	21
Total	**8**	**36**	**44**

About 11 (68.75%) out of 16 patients who did not have AVF, had PH whereas 26 (92.85%) out of the 28 patients with AVF, had PH ($p = 0.002$). About 41 (73.2%) out of the 56 anemia patients, had PH ($p > 0.05$); from the 38 patients with BUN level above 45 mg/dl, 30 (98.94%) had PH ($p > 0.05$); from the 41 patients with serum creatinine higher than 5 mg/dl, 36 (87.8%) had PH ($p < 0.05$); from 9 patients with serum calcium‑phosphorus (Ca × P) product above 55 mg2/dl2, 8 (88.9%) had PH ($p < 0.001$) (Table 4). Thus, patients prone to have PH were patients with serum creatinine >5 mg/dl and Ca × P >55 mg2/dl2. There was no statistically significant association between BUN level above 45 mg/dl and hemoglobin level less than 10 g/dl and PH. There was a direct association between PH and 1) length of CKD duration, 2) calcium phosphorous product 3) serum creatinine, 4) duration of dialysis despite the negative correlation between hemoglobin and PH (Table 4).

Table 4: Biochemical variables and pulmonary hypertension

Variables	PH not present (%)	PH found (%)	Total	P-value
Hb below 10 gm/dl	15 (26.8)	41 (73.2)	56	0.0823
BUN above45 mg/dl	8 (21.1)	30(78.9)	38	0.240
Sr. creat >5 mg/dl	5 (12.2)	36 (87.8)	41	0.020
Ca × P product >55 mg2/dl2	1 (11.1)	8(88.9)	9	<0.001

DISCUSSION

One of the top causes of both mortality and morbidity in CKD patients is cardiovascular disease. Even after adjustment for common risk factors for CAD like diabetes and hypertension there is a progressive increase in mortality risk with worsening of CKD **(13, 14).** Certain patients' profiles were found to have an increased incidence of PHT. This is represented in patients suffering from 1) diabetes, hypertension, 2) left sided heart disease,3) obesity, 4) obstructive sleep apnea, 5) scleroderma, 6) chronic obstructive pulmonary disease.

PH has an estimated prevalence rate of (5-14%) in renal transplantation patients. Whereas the incidence increased to 6-58% in hemodialysis (HD) and 12-42% in patients on peritoneal dialysis (PD) **(15).** Endothelial dysfunction is one among many possible proposed explanations due to increased oxidative stress from uremic toxins, increased flow from arteriovenous fistula, vascular calcification and chronic inflammation. Exposure of blood to the dialysis membrane is believed to cause this chronic inflammation. **(16)**

There was contradicting data regarding the prevalence of PH as Tarras et al. **(17)** detected it to be as low as 26.74% , while Moniruzzaman et al.and Petal et al. **(12, 18)** found it to be in a significantly higher range 60-68.6%.In our study, the prevalence of PH in CKD patients was found to be 60% with Pulmonary Artery Systolic Pressure (PASP) mean value of 38.52 ± 7.32 mmHg with the highest incidence in the HD group (33%) however, age had no effect in the prevalence. Different factors explains the variability of the prevalence rate such as the difference **(12,17-20)** in the ethnicity of the studied population , the stage of CKD, mode of dialysis (HD vs PD), presence of other comorbidities such as COPD, Congestive Heart Failure (CHF), DM and hypertension. Mazdeh et al. **(21)** (p = 0.58) Patel et al. (p = 0.402).[18] and Tarras et al.[17] (p = 0.37),also showed that no effect of age on the prevalence of PHT. As to gender, our study showed higher prevalence of males (p = 0.03) to female which is similar to data published by Moniruzzaman et al. **(12).**

Regarding the association between CKD stages and PH, a statistically significant difference between them ($p < 0.001$) was detected. This indicated that advanced CKD provoked PH. Although all of our patients were in stage III, IV, or V. due to late referrals. Yang *et al.* **(23)** reached a result that PH prevalence is 23.76% (24/101) in stage II and 48.15% (13/27) in GFR below 60 mL/min/1.73 m2 group ($p < 0.05$) showing that pulmonary hypertension can be present before the damping of GFR to <60 ml/min/1.73 m2. This can be due to different reasons such as volume overload, AVF, endothelial dysfunction, vascular calcification and stiffening, severe anemia or exposure and prolonged contact with dialysis membranes. **(24, 25)** synergistic effects of increased PVR, higher cardiac output, and increased Pulmonary Capillary Wedge Pressure (PCWP). This is the exact result as finding by Havlucu et al. **(26)** and Patel et al. **(18).**

As for DM and hypertension contrary to Agarwal et al. (4), there were a definite correlation between diabetes and hypertension with PH (p < 0.001). Fabian et al. **(27)** also concluded a statistically significant association of both diabetes mellitus (p = 0.021) and systemic hypertension (p = 0.0074) with PH. **(28, 29).** Regarding patients on HD, one study showed not just higher prevalence but also higher severity of PH. This is comparable to Moniruzzaman et al. (12) and Kiykim et al. (30) who detected the prevalence to be 68.6% and 68.8% in order. This was also confirmed by Emara et al. (31) and Patel et al. (18, 32). It was also in concordance with Issa et al. (33) and Bozbas et al. (34).

They all studied the effect of HD on prevalence of PH. But no study of them has assessed the correlation between how long the patient has been on HD and severity of PH. In this study, the duration of HD and severity of PH was p< 0.001. The AVF itself contributes to this finding through its increased load of anemia and fluid overload. In this study out of 28 patients with AVF for hemodialysis, 26 had PH, whereas, out of 15 patients not on regular HD, 10 had PH. This result shows there was a strong correlation between HD and PH (p = 0.002).

Agarwal et al.(4) did not find this association contrary to Havlucu et al.(26) This can be attributed to the longevity of AVF and the presence of other variables such as Hemoglobin levels, serum creatinine level, serum k and serum calcium × phosphorus product (Ca × P).

CONCLUSION

This study provides evidence that PH is a common associated disease in CKD patients and is directly proportional with the stage and the duration of CKD. The severity of PH was not only affected but also directly proportional to the duration of hemodialysis.

RECOMMENDATIONS

Pulmonary hypertension should be regularly assessed using echocardiography in CKD patients specially those on regular dialysis

Ethical Approval

The study has not violated any ethical code and all the participating patients had signed an informed consent letter.

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Nil

Conflict of Interest

The authors declare that they have no conflicts of interest.

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