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Incidence and severity of pulmonary hypertension among patients with chronic kidney disease

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ORIGINAL STUDY

Incidence and severity of pulmonary hypertension among patients with chronic kidney disease

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Abstract

Introduction: **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.**

Methods: **In all, 100 patients were included in our study. Transthoracic echo Doppler study was performed to measure pulmonary artery systolic pressure based on tricuspid jet.**

Result: **The prevalence of PH in CKD patients in our study was 60%; prevalence and severity had significant association. The hemodialyzed group showed a higher prevalence of PH with a more severe PH.**

Conclusion: **Our study had provided evidence that PH is a common comorbidity in CKD patients and is directly proportional with the stage and duration of CKD.**

Keywords: Pulmonary hypertension, Chronic kidney disease, Cardiovascular diseases

1. 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 such as 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 comorbidity. It usually involves multiple factors 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 10–14%. Similarly, albuminuria and glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2 have a prevalence of 7% and 3–5%, respectively [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 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 Kidney Disease Improving Global Outcomes as either kidney damage or a reduced GFR to less than 60 ml/min/1.73 m^2 for a period of 3 months at least. Regardless of the cause, the damage to nephrons and reduction of renal mass are usually irreversible and lead to continuous drop in the GFR [8].

The stages of CKD are classified as follows [9]:

(1) Stage 1: kidney damage with normal or elevated GFR (>90 ml/min/1.73 m^2).
(2) Stage 2: mild decrease in GFR (range between 60 and 89 ml/min/1.73 m^2).

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(3) Stage 3a: moderate decrease in GFR (range between 45 and 59 ml/min/1.73 m^2).
(4) Stage 3b: moderate decrease in GFR (range between 30 and 44 ml/min/1.73 m^2).
(5) Stage 4: severe decrease in GFR (range between 15 and 29 ml/min/1.73 m^2).
(6) Stage 5: kidney failure (GFR is below 15 ml/min/1.73 m^2 or dialysis).

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

2. Patients and Methods

This is a retrospective study conducted at Cairo Kidney Center from July 2020 to May 2021.

2.1. Inclusion criteria

We included patients who:

(1) Are classified as stage 3 and above CKD patients (as per KDOQI guidelines): Modification of Diet in Renal Disease (MDRD) formula was used to calculate the eGFR [10,11].
(2) Are 18 years of age or older.
(3) Have normal pulmonary function tests.
(4) Having written informed consent.

2.2. Exclusion criteria

We excluded patients who are:

(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 disease, COPD, scleroderma, and pulmonary embolism) that might cause PH.

We formed a case record form for all patients containing a detailed clinical evaluation and findings including (a) age, (b) sex, (c) CKD with details on etiology and duration and type of dialysis and the presence or absence of arteriovenous fistula (AVF), and (d) associated comorbidity (particularly diabetes and hypertension). It also included laboratory investigations such as (a) complete blood count, (b) serum sodium and potassium, (c) serum aspartate aminotransferase, (d) serum albumin, (e) urine analysis, (f) serum calcium, (g) alanine aminotransferase, (h) serum creatinine and blood urea nitrogen (BUN), (i) serum bilirubin, (j) serum uric acid, and (k) serum phosphate.

All patients had ECGs done and we measured PH by transthoracic echocardiography based on tricuspid regurgitation jet [12]. This was done 4 h after dialysis sessions in dialysis patients. We diagnosed PH when the mean pulmonary artery pressure was found to be 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].

2.3. Statistical analysis

After all the data were collected and revised properly; frequency and percentage were used to express the qualitative data. χ^2 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 the P value of χ^2 was not accepted due to it being a small number.

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, PH grades, etc. When the quantitative data between qualitative variables had more than two subgroups, one-way analysis of variance test was the test used for analysis. This was only after applying the 'normality test' to the data. If the data did not pass the 'normality test,' we analyzed it using Kruskal–Wallis test with application of appropriate post-hoc test.

3. Results

Out of the 100 patients, who participated in the study, 60 (60%) patients had PH. As regards classification of PH in CKD patients, 28 (46.67%) showed moderate PH, 24 (40%) patients showed mild PH, and eight (13.33%) patients showed severe PH.

Age had no effect on the prevalence of PH. Of the total of 60 patients, 37 (61.67%) were males. This was statistically significant ($P = 0.03$). There was statistically significant direct correlation between the stages of CKD and PH ($P < 0.001$). In CKD stages 3, 4, and 5, four (6.67%), 14 (23.33%), and 42 (70%) in row had PH. Twenty-seven (84.37%) out of 31 diabetics had PH whereas from the 26 (57.69%) hypertensive patients, 15 had PH. This indicates a strong significant correlation between hypertension and diabetes mellitus with PH ($P < 0.001$).

Table 1. Duration of chronic kidney disease 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

CKD, chronic kidney disease; PH, pulmonary hypertension.

Table 2. Duration of chronic kidney disease and severity of pulmonary hypertension

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

CKD, chronic kidney disease; PH, pulmonary hypertension.

In patients with CKD duration less than 6 months PH was noted in five (41.67%) out of 12 patients whereas it was noted in 31 (54.38%) out of 57 patients with a CKD period of 6 months to 1 year and in 24 (77.41%) from 31 patients with a CKD period of more than 1 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).

From 24 patients with mild PH, seven (29.16%) had CKD for more than 1 year; from 27 patients with moderate PH, 11 (39.28%) had CKD for more than 1 year; whereas from nine patients with severe PH, six (66.67%) had CKD for more than 1 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).

Out of the 44 patients on regular hemodialysis (HD), 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 eight patients with severe PH, the vast majority, that is, eight (100%) were on HD. This statistically shows how significant is the association between the severity of PH and HD ($P = 0.022$).

Table 3. Duration of hemodialysis 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

HD, hemodialysis; PH, pulmonary hypertension.

As illustrated in Table 3, only one (25%) from four patients on HD less than 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 PH in patients with longer duration of HD ($P < 0.001$). Out of 21 patients on HD for more than 12 months, six (28.6%) had severe PH, whereas from 19 patients on HD for a period of 6–12 months only three (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).

Eleven (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 ($P = 0.002$).

Out of the 56 anemia patients, 41 (73.2%) 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 nine patients with serum calcium–phosphorus (Ca × P) product above 55 mg^2/dl^2, eight (88.9%) had PH ($P < 0.001$) (Table 4). Thus, patients prone to have PH were patients with serum creatinine more than 5 mg/dl and Ca × P more than 55 mg^2/dl^2. 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 (a) length of CKD duration, (b) calcium phosphorous product, (c) serum creatinine, and (d) duration of dialysis despite the negative correlation between hemoglobin and PH (Table 4).

4. Discussion

One of the top causes of both mortality and morbidity in CKD patients is CVD. Even after adjustment for common risk factors for CAD such as diabetes and hypertension, there is a progressive

Table 4. Biochemical variables and pulmonary hypertension

Variables	PH not present (%)	PH found (%)	Total	*P* value
Hb below 10 g/dl	15 (26.8)	41 (73.2)	56	0.0823
BUN above 45 mg/dl	8 (21.1)	30 (78.9)	38	0.240
Serum creatinine >5 mg/dl	5 (12.2)	36 (87.8)	41	0.020
Ca × P product >55 mg^2/dl^2	1 (11.1)	8 (88.9)	9	<0.001

BUN, blood urea nitrogen; PH, pulmonary hypertension.

increase in mortality risk with worsening of CKD [13,14].

Certain patients' profiles were found to have an increased incidence of PH. This is represented in patients suffering from (a) diabetes, hypertension, (b) left-sided heart disease, (c) obesity, (d) obstructive sleep apnea, (e) scleroderma, and (f) 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 HD and 12–42% in patients on peritoneal dialysis [15]. Endothelial dysfunction is one among the many possible proposed explanations due to increased oxidative stress from uremic toxins, increased flow from AVF, 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. [12] and Patel et al. [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 arterial 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 on prevalence. Different factors explain 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. peritoneal dialysis), presence of other comorbidities such as COPD, congestive heart failure, CHF, diabetes mellitus, and hypertension.

Mazdeh et al. [21] ($P = 0.58$), Patel et al. ($P = 0.402$). [19], and Tarras et al. [18] ($P = 0.37$) also showed that there was no effect of age on the prevalence of PH. As to sex, our study showed a higher prevalence of males ($P = 0.03$) to female, which is similar to the data published by Moniruzzaman et al. [12].

Regarding the association between CKD stages and PH we found a statistically significant difference between them ($P < 0.001$), which indicated that advanced CKD provoked PH. However, all of our patients were in stages 3, 4, or 5 due to late referrals. Yang and Bao [22] reached a result that the PH prevalence is 23.76% (24/101) in stage 2 and 48.15% (13/27) in the GFR below 60 ml/min/1.73 m^2 group ($P < 0.05$) showing that PH can be present before the damping of GFR to less than 60 ml/min/1.73 m^2.

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 [23,24], synergistic effects of increased PVR, higher cardiac output, and increased pulmonary capillary wedge pressure (PCWP).

This is an exact similar result as the finding by Havlucu et al. [25] and Patel et al. [18].

As for diabetes mellitus and hypertension contrary to Agarwal [4], there was a definite correlation between diabetes and hypertension with PH ($P < 0.001$). Fabbian et al. [26] also concluded a statistically significant association of both diabetes mellitus ($P = 0.021$) and systemic hypertension ($P = 0.0074$) with PH [3,27].

As regards 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. [28] who detected the prevalence to be 68.6 and 68.8%, respectively. This was also confirmed by Emara et al. [29] and Patel et al. [18,30]. It was also in concordance with Issa et al. [31] and Bozbas et al. [32].

They all studied the effect of HD on the prevalence of PH. But none of the studies has assessed the correlation between how long the patient has been on HD and severity of PH.

In our study, the duration of HD and severity of PH was P value less than 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 HD, 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 [4] did not find this association contrary to Havlucu et al. [25]. 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 Ca × P.

4.1. Conclusions

This study provides an 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 HD.

Ethical approval statement

The institutional committee's ethical criteria were followed during all proceedings. The Ethics Committee approved the study.

Conflicts of interest

There are no conflicts of interest.

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