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Study of Pulmonary Hypertension in Chronic Kidney Disease patients in Sohag University Hospital

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Abstract: Introduction: Early diagnosis and early treatment of PH might improve the long-term outcomes. Therefore, it is crucial to investigate the epidemiology of PH before patients with CKD progress to ESRD. **Patients and Methods:** A cross sectional study was conducted on 228 patients with CKD in Sohag University Hospital. They were divided into two groups: group 1, Included 104 patients with CKD on conservative management (28 patients stage 3, 36 patients stage 4, 40 patients stage 5 NDD-CKD) who attended to out-patient clinic and admitted patients in internal medicine department, group II involved 124 patients with CKD who were maintained on long term regular hemodialysis therapy three times per week. Every patient in both groups underwent a complete two-dimensional and doppler echocardiography study. Tricuspid regurgitation velocity (TRV) was used to determine RV systolic pressure, which is considered equal to systolic pulmonary arterial pressure (SPAP) and compared between both groups. **Results of the study:** The current study showed that PH (SPAP> 35 mmHg) was demonstrated in 24% among 104 patients with CKD stages 3–5 non dialysis dependent with a mean systolic PAP of (41.1± 3.1 mmHg) and (49%) among 124 patients receiving long-term hemodialysis with a mean systolic PAP of (43.1± 7.2 mmHg) and this difference was statistically significant (with a p. value of < 0.001). **Conclusion:** PH is a common finding in CKD patients; the prevalence was highest among patients with ESRD receiving long-term hemodialysis than those on conservative management. Early detection of PH is important in order to avoid the serious consequences of the disease.

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1. Introduction:

Chronic kidney disease (CKD) is an independent risk factor for cardiovascular disease [CVD] and is a global health problem with a high economic cost to health care systems [1]**.** A common co-morbidity in CKD patients and end stage renal disease (ESRD) is pulmonary hypertension (PH) [2]**.** PH in patients with CKD is correlated with an increased risk of hospitalization and deaths [3]**.** Several studies demonstrated that PH is an independent mortality predictor in CKD patients, particularly those undergoing renal replacement therapy (RRT) [4]**.** Patients with CKD may experience co-existing left-sided heart disease, thromboembolic disease, autoimmune diseases, chronic lung disease and liver disease, which are well-established risk factors for the development of PH. However, by itself, CKD, in particular ESRD, indicated causing pulmonary vascular remodeling and PH. Endothelial dysfunction attributable to (elevated oxidative stress from uremic contaminants, chronic inflammation arising from blood exposure to the dialysis membrane), vascular calcification, and elevated flow of arteriovenous fistula (AVF) are potential mechanisms which have been proposed. [5]**.**

Early diagnosis and early treatment of PH can enhance long-term results. Consequently, researching the epidemiology of PH before patients with CKD advance to ESRD is important [6]**.**

2. Patients and Methods:

A cross-sectional research was performed between January 2016 and January 2017 on 228 patients with CKD at Sohag University Hospital.

They have been divided into two groups:

Group I:

Included 104 patients with CKD on conservative management (28 patients stage 3, 36 patients stage 4, 40 patients stage 5 NDD-CKD) who attended to out-patient clinic and admitted patients in internal medicine department.

Group II:

Involved 124 patients with CKD who were underwent on long term regular hemodialysis treatment three times per week in 4-h sessions in hemodialysis unit in Sohag University Hospital. Ethics

committee approval and informed consent have been received**.**

Inclusion criteria:

1-Patients older than 18years.

2- Patients with CKD on medical treatment.

3-- Patients with ESRD on hemodialysis.

Exclusion criteria:

Age less than 18 years, diseases of the lung (chronic obstructive lung disease, chest wall or parenchymal lung disease), Congenital heart diseases, Smokers, Collagen vascular disease, Rheumatic heart disease, pregnancy and Malignancy.

Methods:

A detailed clinical history and examination to all patients.

Laboratory assessment:

Complete blood count, Blood urea nitrogen, Serum creatinine, Liver function examination, lipogram, Serum uric acid, Serum bicarbonate, Serum calcium, phosphorus, Parathyroid hormone level.

Transthoracic Doppler echocardiography:

Each patient in both groups received a complete two-dimensional and doppler echocardiography study (Trans-thorathic Echo (TTE): "Toshiba, NEMIO30"). In group II, TTE was done within 4 hrs after completion of dialysis on the day after dialysis when patients reach the "dry weight" recommended by nephrologists on clinical review, which include BP and weight, to prevent overestimation of PAP owing to volume overload to assess:

1-Dimensions.

2-Left ventricular function.

3-Valvular lesions and its degree.

4-Estimate pulmonary artery pressure:

In the absence of pulmonary outflow tract blocking and/or pulmonary valve stenosis, tricuspid regurgitation velocity (TRV) was used to assess RV systolic pressure, considered equivalent to systolic pulmonary arterial pressure (SPAP). This is achieved by using the modified Bernoulli equation to calculate the systolic trans-tricuspid gradient and then adding calculated right atrial pressure (RAP) which estimated from IVC and its collapsibility [7]**.**

Statistical analysis:

Statistical package for social sciences (IBM-SPSS), version 24 for statistical data processing, IBM-Chicago, USA (May 2016) has been utilized. The data is represented as mean, standard deviation (SD), number and percentage. As a descriptive value for quantitative data, average and standard deviation have been utilized, whereas number and percentage have been utilized to characterize qualitative data.

For comparisons among qualitative variables, the **Chi-Square test** has been used. The **Shapiro–Wilk test** examined quantitative data for normality.

3. Results:

The most prevalent etiologies of kidney failure in both subgroups became diabetes mellitus and hypertension. Data on 25 (out of 104) PH patients had been contrasted to the 79 patients without PH in conservative treatment patients. There was a highly statistically significant increase in age, serum phosphorous, serum parathyroid hormone and highly statistically significant decrease in serum calcium, HB level, Hematocrit % in PH subgroup relative to normal PAP subgroup. There is no statistically significant difference among both subgroups regarding ejection fraction. There is a highly statistically significant difference between both subgroups regarding RVH which demonstrated among 20 patients (80%) in PH subgroup comparing to 10 patients (12.7%) without PH subgroup. LVH which demonstrated among 19 patients (76%) in PH subgroup comparing to 34 patients (43 %) without PH subgroup, left atrial diameter, LVEDD, LVESD were higher in patients with PH subgroup comparing patients without PH subgroup. Valvular calcification was demonstrated among 6 patients (24 %) in PH subgroup comparing to one patient (1.3%) without PH subgroup with statistically significant difference (p-value< 0.001). Diastolic dysfunction was demonstrated among 19 patients (76%) with PH subgroup comparing to 29 patients (36.7%) without PH subgroup with highly statistically difference between both subgroups. (p-value < 0.001). The data for 61 (out of 124) PH patients have been contrasted with 63 non-PH patients for hemodialysis patients. Brachial AVF; 43 out of 61 sufferers (70.5 %) constitute the majority of sufferers in the PH subgroup and radial AVF; 43 out of 63 (68.3 %) constitute the majority of sufferers in the normal PAP hemodialysis subgroup. A highly statistically substantial increase in age, dialysis treatment length, serum phosphorus, serum parathyroid hormone and a highly statistically substantial decrease in serum calcium, HB level, Hematocrit % in PH subgroup relative to the normal PAP subgroup was observed. There is no statistically significant difference among both subgroups regarding ejection fraction. There is a highly statistically significant difference between both subgroups regarding RVH which demonstrated among 45 patients (73.8%) in PH subgroup comparing to 14 patients (22.2%) without PH subgroup. LVH which demonstrated among 40 patients (65.6%) in PH subgroup comparing to 21 patients (33.3%) without PH subgroup, left atrial diameter, LVEDD, LVESD were higher in patients with PH subgroup comparing patients without PH subgroup. Valvular calcification was demonstrated among 21 patients (34.4%) in PH subgroup comparing to 3 patients (4.8%) without PH subgroup with statistically significant difference (p-value< 0.001). Diastolic dysfunction was

demonstrated among 40 patients (65.6%) with PH subgroup comparing to 19 patients (30.2%) without PH subgroup with highly statistically difference between both subgroups. (p-value < 0.001).

Table (1): Comparison between patients in all studied groups regarding clinical data:

Parameter	Hemodialysis patients		P-value	patients not on dialysis		P-value
	Without PH (N= 63)	With PH (N= 61)		Without PH (N= 79)	With PH (N= 25)	
Age (year)						
• Mean± S.D.	38.9 ± 10.4	48 ± 10.8	<0.001	49.6 ± 9.4	54.4 ± 7.8	< 0.001
• Median (Range)	40 (19 – 62)	45 (30 – 77)		49 (35 – 71)	54 (43 – 65)	
Sex						
• Males (%)	44 (69.8%)	41 (67.2%)	0.753	41 (51.9%)	15 (60%)	0.479
• Females (%)	19 (30.2%)	20 (32.8%)		38 (48.1%)	10 (40%)	
Body mass index	28.8 ± 6.2	26.4 ± 4.9	> 0.05	27.8 ± 6.2	25.4 ± 4.9	> 0.05
Duration of CKD (year)						
• Mean± S.D.				1.9 ± 0.89	3.2 ± 1.2	< 0.001
Median (Range)				2 (1 – 5)	3 (1 – 5)	
Duration of hemodialysis (year)						
• Mean± S.D.	4.4 ± 1.7	8.5 ± 2.3	< 0.001			
• Median (Range)	5 (1 – 11)	8 (1 – 16)				
Access location						
• Brachial (%)	20 (31.7%)	43 (70.5%)	< 0.001			
• Radial (%)	43 (68.3%)	18 (29.5%)				

Table (2): Comparison between patients in all studied groups regarding HB level, HCT:

Parameter	Hemodialysis patients		P-value	patients not on dialysis		P-value
	Without PH (N= 63)	With PH (N= 61)		Without PH (N= 79)	With PH (N= 25)	
HB (g/dl)						
• Mean± S.D.	10.4 ± 0.9	8.4 ± 1.2	< 0.001	10.3 ± 0.9	8.5 ± 1.2	< 0.001
• Median (Rang)	10.5 (7.9 – 13.8)	8.5 (5.6 – 12)		10.7 (8.5 – 11.5)	8.5 (7 – 10.5)	
HCT (%)						
• Mean± S.D.	30.8 ± 2.09	29.8 ± 3.9	< 0.002	30.4 ± 1.8	28.7 ± 1.4	< 0.001
• Median (Range)	30 (26 – 41)	29 (20.1 – 47)		30 (28 – 33)	29 (26 – 31)	

Table (3): Comparison between patients in all studied groups regarding PTH level, serum calcium, serum phosphorus:

Parameter	Hemodialysis patients		P-value	patients not on dialysis		P-value
	Without PH (N= 63)	With PH (N= 61)		Without PH (N= 79)	With PH (N= 25)	
PTH level (pg/ml)						
• Mean± S.D.	325.1 ± 362.9	895.1 ± 527.4	< 0.001	98.3 ± 33.6	294.8 ± 62.5	< 0.001
• Median (Range)	210 (65 – 1675)	962 (75 – 1900)		97.5 (54 – 158)	317 (170 – 352)	
Serum Calcium (mg/dl)						
• Mean± S.D.	9.6 ± 1.4	8.9 ± 0.9	< 0.001	10.2 ± 1.1	9.1 ± 0.6	< 0.001
• Median (Range)	9.1 (7.9 – 15.3)	8.8 (6.6 – 12)		10 (9 – 12)	9 (8 – 10)	
Serum Po4 (mg/dl)						
• Mean± S.D.	3.7 ± 0.6	4.4 ± 0.7	< 0.001	3.7 ± 0.4	4.4 ± 0.5	< 0.001
• Median (Range)	3.6 (0.8 – 5)	4.2 (3.5 – 8.1)		3.7 (3 – 5)	4 (4 –5)	

Table (4): Comparison of hemodialysis patients (with or without pulmonary hypertension) regarding Echocardiography findings:

Parameter	Hemodialysis patients		P-value
	Without PH (N= 63)	With PH (N= 61)	
Right side:			
Right ventricular hypertrophy: No (%) Yes (%)	 49 (77.8%) 14 (22.2%)	 16 (26.2%) 45 (73.8%)	< 0.001
Left ventricle:			
left ventricular hypertrophy No (%) Yes (%)	 42 (66.7%) 21 (33.3%)	 21 (34.4%) 40 (65.6%)	< 0.001
LVEDd (cm) Mean± S.D. Median (Range)	 4.6 ± 0.8 4.6 (3.3 – 6.9)	 4.9 ± 1.01 5 (2.75 – 6.7)	0.048
LVESd (cm) Mean± S.D. Median (Range)	 3.1 ± 0.7 3 (2 – 5.3)	 3.6 ± 0.6 3.5 (2.1 – 6)	< 0.001
Ejection fraction (%) Mean± S.D. Median (Range)	 58.4 ± 4.2 60 (47 – 66)	 57.7 ± 6.3 60 (33 – 67)	0.685
Diastolic dysfunction No (%) Yes (%)	 44 (69.8%) 19 (30.2%)	 21 (34.4%) 40 (65.6%)	< 0.001
Left atrium:			
Left atrium diameter (cm) Mean± S.D. Median (Range)	 3.4 ± 0.5 3.4 (2.3 – 4.5)	 3.8 ± 0.7 3.7 (2.5 – 5.4)	0.002
Others:			
Valvular calcification No (%) Yes (%)	 60 (95.2%) 3 (4.8%)	 40 (65.6%) 21 (34.4%)	< 0.001

Table (5): Comparison between patienets on conservative management (with or without pulmonary hypertension) regarding Echocardiography findings:

Parameter	patients not on dialysis		P-value
	Without PH (N= 79)	With PH (N= 25)	
Right side:			
Right ventricular hypertrophy No (%) Yes (%)	 69 (87.3%) 10 (12.7%)	 5 (20%) 20 (80%)	< 0.001
Left ventricle:			
left ventricular hypertrophy No (%) Yes (%)	 45 (57%) 34 (43%)	 6 (24%) 19 (76%)	0.004
LVEDD (cm) Mean± S.D. Median (Range)	 4.8 ± 0.8 4.6 (3.02 – 7.09)	 5.3 ± 0.5 5.2 (4.5 – 6.7)	< 0.001
LVESD (cm)	3.3 ± 0.9	4.2 ± 0.4	< 0.001
Mean± S.D. Median (Range)	 3.1 (1.5 – 5.6)	 4(4 – 5.4)	
Ejection fraction (%) Mean± S.D. Median (Range)	 59.4 ± 5.9 60 (36 – 69)	 59.9 ± 3.9 60 (50 – 68)	0.644
Diastolic dysfunction No (%) Yes (%)	 50(63.3%) 29 (36.7%)	 6 (24%) 19 (76%)	0.001
Left atrium:			
Left atrium diameter (cm) Mean± S.D. Median (Range)	 3.4 ± 0.6 3.2 (2 – 5.4)	 4.2 ± 0.4 4 (3.5 – 5.7)	< 0.001
Others:			
Valvular calcification No (%) Yes (%)	 78 (98.7%) 1 (1.3%)	 19 (76%) 6 (24%)	< 0.001

4. Discussion:

The current study reported that PH (SPAP> 35 mmHg) was demonstrated in 24% among 104 patients with CKD stages 3–5 non dialysis dependent with a mean systolic PAP of (41.1± 3.1 mmHg) and (49%) among 124 patients undergoing long-term hemodialysis with a mean systolic PAP of (43.1± 7.2 mmHg). This is in concordance with **Yigla et al. (2003)** who reported that the prevalence of PH was 39.7% in HD patients with a mean (44± 7 mmHg). In addition, **Mahdavi-Mazdeh et al. (2008)** reported that the prevalence of PH ranges from 30–40% as detected by Doppler echocardiography in HD patients. Also, **Abdelwhab et al. (2008)** demonstrated that PH was found in 44.4% in HD patients. Similarly, **Bolignano et al. (2015)** reported that the prevalence of PH was 23% in a study that included 468 CKD patients. Also, **Javier Reque et al. (2017)** reported that the prevalence of PH was 26.6% in patients with CKD stages 3–5 non dialysis dependent. Several factors could explain the higher prevalence of PH in CKD, where cardiac output, pulmonary vascular resistance and pulmonary capillary wedge pressure are the primary factors of pulmonary arterial pressure, all of which could be changed to a variable degree in CKD patients (**Sise et al. 2013).** Therefore some CKD patients are affected by a rise in cardiac output attributable to hyperdynamic circulation secondary to AVF, anemia and volume overload (**Stauffer et al., 2014) (Tsai et al., 2014).** This study show a highly statistically significant increase in age in PH subgroup in hemodialysis group as well as conservative group. Similar to Magdy **et al. (2013)** who found a highly statistically significant increase in age, a positive significant correlation between PAP and age. The present study found no significant difference between gender and development of PH. Similarly, **Tarrass et al. (2006)** and **Kumbar et al. (2007)** stated that there was no difference among gender and development of PH. In the current study there is a highly statistically significant increase in duration of CKD in PH subgroup in conservative group. These findings are consistent with **Havlucu et al. (2007)**, who noticed

that the period of CKD was associated positively with PAP.

A highly statistically substantial increase in the duration of dialysis treatment in the PH subgroup of the hemodialysis group was observed in the current research. Similar findings were demonstrated by **Jawad (2009)** who found that the presence of PH was related to long duration of hemodialysis. In addition, **Abdallah et al. (2010)** showed that in patients undergoing hemodialysis, CKD duration and AV fistula duration were positively associated with systolic PAP. In contrast, **Amin et al. (2003)** and **Tarrass et al. (2006)** confirmed that there was no substantial difference in dialysis time among PH patients and those without PH. In this study there were 43 out of 61 patients (70.5%) with brachial AVF location had PH, compared to 18 patients (29.5%) with radial AVF location had PH among hemodialysis patients, which was a highly statistically significant difference ($p < 0.001$). Brachial AVF was also reported by **Magdy et al. (2013);** 23 out of 27 patients (85.18 %) constitute the majority of sufferers in the PH subgroup and radial AVF; 23 out of 38 (60.52 %) constitute the majority of sufferers in the normal PAP subgroup of HD sufferers in his study. Higher blood flow from AVF, higher COP, increased sympathetic activity, leading to an increase in myocardial contractility and heart rate, increased blood flow from the lungs, large vessel fistula formation. **Tarrass et al. (2006),** on the other hand, found that the influence of the position of AVF was not statistically significant**.** The current study demonstrated a highly statistically significant decrease in hemoglobin level, haematocrite level in PH subgroup in HD group as well as conservative group. Similarly, **Yigla et al. (2003)** contrasted data on 23 PH patients undergoing HD with 35 non-PH patients undergoing HD, and found significantly lower levels of hemoglobin and hematocrit in the PH subgroup. Also, **Buemi et al. (2007)** reported that the association between lower hemoglobin levels and PH may be explained by tissue hypoxia caused by lower hemoglobin levels can raise PAP in CKD. The current study demonstrated a highly statistically significant increase in parathyroid hormone level in PH subgroup in HD group as well as conservative group.

Similarly, **Mousavi et al. (2014)** reported that a significant increase in parathyroid hormone level in PH compared with normal pulmonary artery pressure in HD patients. Also, **Demir et al. (2013)** reported that hyperparathyroidism was associated with higher pulmonary artery pressure as a result of low vitamin D levels. In addition, **Genctoy et al., (2015)** observed that in sufferers with PH, the parathyroid hormone level was substantially elevated relative to people with normal pulmonary artery pressure.

Amin et al. (2003), on the other hand, indicated that no significant variation occurred among sufferers with PH and those without PH in HD patients regarding PTH level [420± 512 pg/mL vs 354 ± 519 pg/mL]. **Unal et al. (2010)** also confirmed that there was no substantial variation in PTH among sufferers with and without PH in CKD. The current study demonstrated a highly statistically significant increase in serum phosphorus level in PH subgroup in HD as well as conservative group. Similarly, **Magdy et al. (2013)** reported that there is a positive significant correlation between PAP and serum phosphorous. On the other hand, **Amin et al. (2003)** stated that there was no substantial variation among sufferers with PH and those without PH in HD regarding to serum phosphorus. The current study demonstrated that a highly statistically substantial decrease in serum calcium in PH subgroup in HD patients as well as conservative group. Similarly, **Kumbar et al. (2007**) reported that the serum calcium level was significantly lower in the sufferers with PH. On the other hand, **Amin et al. (2003)** stated that there was no significant variation among sufferers with PH and those without PH in HD regarding serum calcium (9.6 ±2 mg/dL vs 10 ± 2 mg/dL). The current study reported a highly statistically significant increase in LVH in PH subgroup in HD as well as conservative group.

In CKD patients, LVH is the most often seen cardiac abnormality (**Park et al., 2012**). LVH is significantly associated with CVD events and mortality **(Paoletti et al., 2004)**. The most significant factor leading to increased afterload in CKD patients is vascular calcification and arterial hypertension. In addition, anemia, oxidative stress, renin-angiotensin-aldosterone system activation, uremic toxins, and CKD-MBD including serum phosphate increase, PTH level, lead to LVH **(Di Lullo et al., 2015).**

The current study reported no statistically significant difference in systolic function in PH subgroup in HD as well as conservative group. The current study demonstrated a highly statistically significant increase in left atrial diameter in PH subgroup in HD as well as conservative group. The present study demonstrated a highly statistically significant increase in diastolic dysfunction in PH subgroup in HD as well as conservative group. Similarly, **Sun Chul Kim et al. (2015)** found that left atrial diameter was strongly correlated with PH, this indicates that, regardless of myocardial dysfunction in dialysis patients, chronic volume overload becomes a risk factor for PH.

Kawar et al. (2013) also reported that left atrial diameter was a good indicator of diastolic dysfunction, and these results indicate that diastolic dysfunction could be an important mechanism for PH in this group of patients. Chronic fluid overload is likely to

exacerbate the diastolic dysfunction in advanced CKD patients. The present study found a significant increase in LVEDD, LVESD in PH group in HD group as well as conservative group.

Also, **Agarwal, (2012)** reported that a significant increase in LVEDD, Chronic volume overload, the impact of AVF on the heart, or poor myocardial efficiency may be expressed by LVESD.

There is a highly statistically significant difference in valvular calcification which was higher in PH subgroup in HD. Similarly, **Leskinen et al., (2009)** recorded that in NDD-CKD patients, the incidence of mitral annulus calcification (MAC) in combination with aortic valve calcification (AVC) or mitral valve calcification (MVC) was 17% and 27%, and in dialysis patients, 31% and 50%, respectively.

Limitation of the study:

We only measured the PASP by echocardiography, rather than specifically calculating it by RHC. Due to its invasive nature, most studies use the estimated PASP due to its non-invasive nature and the good association with RHC by transthoracic echocardiography. No information has been gathered on volume status or body composition analysis by bio impedance.

Conclusion:

- PH is a frequent condition in CKD patients, with the highest prevalence between ESRD patients undergoing long-term hemodialysis relative to conservative patients.
- In order to avoid the serious consequences of the disease, early detection of PH is necessary.

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