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"Assessment of Secondary Hyperparathyroidism as a Cause of Pulmonary Hypertension among End Stage Renal Disease Patients on Regular Hemodialysis "

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ABSTRACT:

Background: End-stage renal disease can result in several systemic consequences that pose a significant risk to life, such as cardiovascular disorders. Pulmonary arterial hypertension, characterized by increased blood pressure in the pulmonary artery, poses a significant risk for both morbidity and mortality in individuals with end-stage renal disease (ESRD). **Aim of the study:** The aim of the current study was to evaluate association between hyperparathyroidism and incidence of pulmonary hypertension among haemodialysis patients. **Methods:** This study was performed on 100 haemodialysis patients; they were divided according to incidence of pulmonary hypertension into 2 groups: 63 pulmonary hypertension patients and 37 patients without pulmonary hypertension. **Results:** The most reported leading cause of end- stage renal disease was hypertension (65%), analgesic nephropathy (11%) and diabetic nephropathy (9%). About 27% of patients had residual urine output.The included patients received hemodialysis for about 3.06 ± 1.5 years with average ultrafiltration rate 3.3 ± 1.15 L. About 96% of patients received hemodialysis via A- v fistula and mean A- v fistula flow volume was 1111.7 ± 434.1. **Conclusion:** Disturbance in parathyroid release significantly affected incidence of pulmonary hypertension. Also, hypoparathyroidism is associated with increased incidence rate of pulmonary hypertension.

Key Words: chronic kidney disease, end-stage renal disease, haemodialysis, hyperparathyroidism, pulmonary hypertension.

INTRODUCTION:

Chronic kidney disease (CKD) is a significant global health problem, affecting almost 10% of the world's population (Senan et al., 2021). Chronic kidney disease is characterized by changes in the structure or function of the kidneys that last for more than three months and have health concerns. Chronic kidney disease is known to be categorized according to its cause, glomerular filtration rate (GFR), and stage of albuminuria **(Levey et al., 2020)**.

It is defined by an irreversible decline in its functioning, including the inability to maintain homeostasis. End-stage renal disease (ESRD) is a condition characterized by severe kidney impairment, requiring the use of renal replacement therapy such as dialysis (hemodialysis, peritoneal) or kidney transplant **(Kumar et al., 2018)**.

Patients undergoing frequent haemodialysis are significantly more susceptible to cardiovascular disease (CVD)-related mortality compared to the general population. In fact, their risk of death due to CVD is ten times higher (Loutradis et al., 2018).

Pulmonary hypertension (PH) is a significant cardiovascular consequence that occurs in patients with end-stage renal disease who are undergoing haemodialysis (HD) (Tudoran et al., 2020). Pulmonary hypertension is characterized by increased pressures in the pulmonary artery (PAP) with mean values exceeding 25 mmHg during periods of rest. Pulmonary hypertension is categorized into five distinct clinical groupings. The classification of PH in renal failure is categorized as group 5, and its underlying mechanisms are not well understood and may involve multiple factors **(Nagel et al., 2019 and Tudoran et al., 2019).**

Pulmonary hypertension is a progressive and life-threatening condition that occurs in conjunction with either left or right ventricular failure. The long-term complication of right ventricular dysfunction, which results in right-sided heart failure, has a significant impact on the survival of patients in this cohort **(Navaneethan et al., 2014).**

Since its first identification thirty years ago, numerous echocardiogram-based studies have examined the frequency of pulmonary hypertension in individuals with renal illness. Nevertheless, the actual prevalence and characteristics of pulmonary hypertension in the chronic kidney disease and end-stage renal disease population remain uncertain due to the limitations of existing studies. These studies are primarily retrospective in nature, suffer from referral bias, have small sample sizes, use inconsistent definitions of PH, and, most importantly, lack invasive hemodynamic measurements to confirm the presence and assess the severity of PH. among a recent meta-analysis conducted by Shang et al. (2018), the

researchers examined the frequency of pulmonary hypertension among individuals with chronic kidney disease who were not undergoing hemodialysis.

Despite the presence of variability, the overall frequency of PH was a remarkable 32%. The prevalence of pulmonary hypertension (PH) in various stages of chronic kidney disease (CKD) was as follows: stage 1 (10%), stage 2 (13%), stage 3 (28%), stage 4 (30%), and stage 5 (30%). In a similar vein, **Tang et al. (2018)** conducted a meta-analysis that revealed a prevalence rate of 21-27% among individuals with chronic kidney disease (CKD).

Severe anemia, excessive fluid accumulation, the presence of an abnormal connection between an artery and a vein, exposure to the dialysis membrane, malfunction of the cells lining the blood vessels, and the hardening and calcification of blood vessels, all contribute to the development of pulmonary hypertension in patients with chronic renal disease. The prevalence of pulmonary hypertension in hemodialysis patients is reported to be 58.82% **(Zhang et al., 2018).**

Multiple animal studies indicate a robust correlation between hyperparathyroidism and pulmonary hypertension. The condition of hyperparathyroidism is linked to the development of pulmonary vascular calcification and pulmonary hypertension (PH) in a dog model with chronic kidney failure. Additionally, there is an increased occurrence of PH and a relationship between PH and hyperparathyroidism in patients with pre-dialysis chronic kidney disease (CKD) and those undergoing hemodialysis **(Eskandraian et ., al 2019).**

Patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD) may experience pulmonary hypertension (PH), which can lead to irreversible heart failure and mortality. Therefore, it is crucial to be aware of this complication and to assess patients using echocardiography. This technique provides the opportunity to precisely assess the function of the left and right ventricles, as well as the pulmonary artery pressure (PAPs) and pulmonary vascular resistance (PVR), without the potential dangers associated with invasive procedures such as right heart catheterization **(Naing et al., 2017).**

The aim of the current study is to evaluate the association between hyperparathyroidism and incidence of pulmonary hypertension among haemodialysis patients.

PATIENTS AND METHODS

A cross sectional, analytical study was conducted in Port-Fouad general hospital (El Hayat) at Nephrology Unit on 100 patients on 2023 with ESRD on regular HD for at least 6 months. Diagnosis of pulmonary HTN was based on pulmonary artery pressure equal or more than 25 mmHg by ECHO assessment and hyperparathyroidism >300 pmol/L.

The study was approved by the local Institutional Review Board (under IRB No. ERN: MED(1/2/2023)s.no(75)MED/NEP809_004). Patients were treated according to the principles of declaration of Helsinki.

Patients were divided into two groups:

No pulmonary hypertension group (n = 37) which include patients with PAP equal or less than 25 mmHg and Pulmonary hypertension group (n = 63) which include patients with PAP equal or more than 25 mmHg.

Inclusion criteria: All ESRD patients undergoing regular hemodialysis in hemodialysis units in Port-Fouad for at least 6 months after applying exclusion criteria.

Exclusion criteria: Patients with IHD, smoking, any history of known chronic obstructive airway disease, patients with chronic atrial fibrillation, uncontrolled hypertension, adherence problems to diet and medication, active malignancies and inflammation, and infectious or hepatic diseases. No patient is taking fish oil, active vitamin D, or derivatives at the time of study. Patients with high flow AV fistula > 2000 mg/min

Methods:

Complete history taking: Name, age, sex, smoking, duration of CKD and hemodialysis, history of comorbidities as DM, HTN, IHD, glomerular nephritis and chest diseases. Cause of ESRD. COVID 19 vaccination status and previous infection. The dialysis access, duration of dialysis, number of sessions per week, duration of each sessions, average ultrafiltration, anticoagulation, clotting events, residual urine output and number of previous AV fistula will be assessed.

Clinical examinations: Height will be measured on standing meter without shoes and cap in cm and later on converted to meters. Weight will be measured bathroom scale rounded 0.1 kg without shoes and in light clothes. Clinical examinations of chest, heart, abdomen and peripheral pulsation

Investigations: Routine laboratory investigations including CBC with differential count, ferritin, liver and kidney functions, lipid profile, calcium, phosphorus, PTH, and vitamin D, dialysis efficiency by kt/v equation and urea reduction ratio (URR), inflammatory markers (ESR and CRP), PT, PTT and INR. ECG and transthoracic echocardiography will be done for all patients. All echocardiographic examinations will be performed post dialysisas soon as possible (in their dry weight). Assessment of LV mass index (LVMI), ejection fraction (EF), tricuspid annular plane systolic excursion (TAPSE), right atrial (RA), right ventricle (RV) size, CO, the velocity of the tricuspid regurgitation (TRV), and pulmonary vascular resistance (PVR). Also, assessment of AVF flow volume (FV) in mL/min.

Statistical analysis:

All results will be statistically analysed and tabulated., Each variable will be coded to facilitate the transfer of data, These codes will be entered into computer through Statistical Package for Social Science (SPSS) version 26 where all statistical analyses will be performed, Associations between the outcome measures and different components of the program were tested for significance by using Chi-square test, Statistical significance is determined at 95% level of confidence (i.e. differences will be considered significant if $P < 0.05$), Data was be presented as required according to the type of variables.

RESULTS

The present study included 100 haemodialysis and CKD patients with mean age 55.1 ± 14.8 years and male predominance (57%). Mean body weight of the included patients was 84.2 ± 18.4 Kg and mean height was 166.3 ± 9.3 cm. Mean BMI was 30.1 ± 5.4 Kg/m2. About 60% of the included patients were smokers. Hypertension was a consistent finding in 49% of patients followed by diabetes in 18% of patients. Mean CKD duration was 3.06 ± 1.5 years and mean HD duration was 3.3 ± 1.15 years. Average UF rate was 3.3 ± 1.15 litters. About 96% received HD via a-v fistula. Only 4 patients did not have any fistula. On the other side, there was 7 patients had 2 A- v fistula, one failed and one was functioning. The remain 89 patients had 1 functioning A- v fistula.

The main reported original kidney disease among the included patients was hypertension (65%) followed by analgesic nephropathy (11%) and diabetic nephropathy (9%). Other causes were reported at lower frequencies. According to iPTH status, 19% of patients had hypoparathyroidism, 41% of patients had hyperparathyroidism while 40% of patients had normal iPTH levels.All patients underwent Echocardiographic evaluation. Mean LVMI was 281.9 ± 70, mean EF was 55.9 ± 5.8%, mean TAPSE was 20 ± 2.9. Mean right atrium size was 35.8 ± 4.3 mm, mean right ventricle size was 43.5 ± 4.9 mm. Mean CO was 5.9 ± 1.6 L. Mean TR velocity was 3.35 ± 4.3. Mean pulmonary vascular resistance was 2.7 ± 0.8 and mean pulmonary artery pressure 43.2 ± 17.8. Among the included patients, pulmonary hypertension was diagnosed in 63% of patients.Mean A- v fistula flow volume was 1111.7 ± 434.1.

Patients were divided into 2 groups according to diagnosis of pulmonary hypertension. Pulmonary hypertension group included 63 patients and no pulmonary hypertension group included 37 patients. Both groups had comparable age and gender distribution. Mean body weight and BMI was higher among pulmonary hypertension group with statistically significant differences (p= 0.04; 0.037 respectively). Smoking rate was higher among

pulmonary hypertension group than no pulmonary hypertension group with statistically significant difference (p= 0.028) (Table 1).

Diabetes incidence was higher among pulmonary hypertension group than no pulmonary hypertension group with statistically significant difference. There were no statistically significant differences between pulmonary and no pulmonary hypertension groups as regard systemic hypertension, dialysis duration, average UFR and number of A- v fistula (Table 2).

Mean INR levels were lower among pulmonary hypertension group than no pulmonary hypertension group with statistically significant difference (p= 0.01). Mean cholesterol, triglyceride and LDL levels were higher among pulmonary hypertension patients than no hypertension patients with no statistically significant differences while HDL was lower among pulmonary hypertension patients than no pulmonary hypertension patients with statistically significant differences (p=0.02; 0.04; 0.002 and <0.001 respectively). Intact PTH median was higher among pulmonary hypertension patients than no pulmonary hypertension patients with statistically significant differences. Lower range was lower and upper range was higher among pulmonary hypertension group (= 0.007) (Table 3).

Most of no pulmonary hypertension patients had normal iPTH levels (p= 0.02) while higher percent of pulmonary hypertension patients had either low or high iPTH with statistically significant differences (p= 0.033; 0.03 respectively). There were no statistically significant differences between both groups as regard presence of residual urine output (Table 4).

TR velocity and pulmonary artery pressure mean values were higher among pulmonary hypertension group than no pulmonary hypertension group with statistically significant differences. Cardiac output is higher significantly among patients with no pulmonary hypertension than patients with pulmonary hypertension with significant differences (p= 0.018). Otherwise, there were no statistically significant differences between both groups as regard other echo parameters. Also, there was no statistically significant difference between both groups as regard A- V fistula flow volume (Table 5).

Table (1): Comparison between patients with and without pulmonary hypertension as regard demographic data:

	No pulmonary hypertension (n= 37)	Pulmonary hypertension (n= 63)	Test of significance	P value
Gender No. (%) - Male - Female	 17 (45.9%) 20 (54.1%)	 40 (63.5%) 23 (36.5%)	$X^2 = 2.9$	0.087
Age (years) Mean ± SD	52.6 ± 14.86	56.6 ± 14.7	t= -1.3	0.2
Height (kg) Mean ± SD	163.9 ± 9.4	168.7 ± 8.8	t= -2.1	***0.04***
Weight (cm) Mean ± SD	77.5 ± 14.15	88.2 ± 19.5	t= -2.8	***0.005***
Body mass index (kg/m²) Mean ± SD	28.6 ± 4.4	30.9 ± 5.8	t= -2.2	***0.037***
Smokers No. (%)	17 (45.9%)	43 (68.3%)	$X^2 = 4.8$	***0.028***

t: student t- test; X^2: Chi-square test; Level of significance < 0.05.

Table (2): Comparison between patients with and without pulmonary hypertension as regard associated co morbidities and dialysis data:

	No pulmonary hypertension (n= 37)	Pulmonary hypertension (n= 63)	Test of significance	P value
Diabetes No. (%)	1 (2.7%)	17 (27%)	$X^2 = 9.3$	***0.002***
Hypertension No. (%)	15 (40.5%)	34 (54%)	$X^2 = 1.68$	0.19
Dialysis duration (years) Mean ± SD	3.6 ± 1.89	2.68 ± 1.2	t= 1.28	0.22
Average ultrafiltration (L) Mean ± SD	3.27 ± 1.15	3.33 ± 1.16	t= -0.25	0.79
Number of A- v fistula No. (%) - No A- v fistula - 1 A- v fistula - 2 A- v fistula	 1 (2.7%) 32 (86.5%) 4 (10.8%)	 3 (4.8%) 57 (90.5%) 3 (4.8%)	$X^2 = 1.5$	0.47

t: Student t- test; X^2: Chi-square test; Level of significance < 0.05

Table (3): Comparison between patients with and without pulmonary hypertensionas regard laboratory findings:

	No pulmonary hypertension (n= 37) Mean ± SD	Pulmonary hypertension (n= 63) Mean ± SD	(t)	P value
Hemoglobin (g/dL)	10.8 ± 1.8	10.7 ± 1.6	0.41	0.68
White blood cells (/mm^3)	6.9 ± 1.7	7.03 ± 2.5	-0.19	0.85
Platelets (/mm^3)	195.8 ± 62.9	174.6 ± 50.1	1.86	0.067
Prothrombin time (seconds)	13.4 ± 0.09	13.2 ± 0.4	2.4	0.4
Partial thromboplastin time (seconds)	32.8 ± 6.9	32.06 ± 5.3	0.58	0.56
International normalization ratio (INR) (%)	1.05 ± 0.09	1.02 ± 0.03	2.6	0.09
Erythrocyte sedimentation rate	42.2 ± 5.3	41.7 ± 4.4	0.065	0.95
C- reactive protein (mg/dL)	34.6 ± 5.2	31.8 ± 4.3	0.4	0.69
Alanine aminotransferase (IU/L)	15.8 ± 6.4	17 ± 6.014	-0.6	0.54
Aspartate aminotransferase (IU/L)	17.6 ± 8.3	17.5 ± 8.2	0.07	0.9
Albumin (g/dL)	4.1 ± 0.4	4.13 ± 0.4	-0.64	0.5
Creatinine (mg/dL)	8.9 ± 2.5	8.8 ± 2.3	-0.03	0.98
Cholesterol (mg/dL)	180.5 ± 43.9	204.3 ± 55.5	2.4	***0.02***
Triglyceride (mg/dL)	161.3 ± 69.1	199.8 ± 90.2	-2.1	***0.04***
High density lipoprotein (mg/dL)	47.8 ± 9.6	41.4 ± 8.7	3.4	***<0.001***
Low density lipoprotein (mg/dL)	99.3 ± 30.8	124.9 ± 48.1	-3.2	***0.002***
Ferritin (mg/dL)	715.2 ± 333	759.6 ± 380	-0.45	0.65
Calcium (mg/dL)	9.1 ± 0.9	8.9 ± 1.02	0.73	0.47
Phosphorus (mg/dL)	6.5 ± 2.2	6.1 ± 1.8	0.99	0.3
iPTH (pg/dL) Median (min, max)	382 (84.4, 1613)	399 (21.1, 2456)	U= -86	***0.007***
Vitamin D	20.5 ± 10	18.3 ± 9	1.007	0.32
Urea (Before) (mg/dL)	127.6 ± 28.8	137.4 ± 29.6	-1.6	0.11
Urea (After) (mg/dL)	47.4 ± 16.8	51.3 ± 16.7	-1.13	0.26
Urea reduction ratio (%)	62.2 ± 12.9	62.15 ± 10.8	0.04	0.97
Kt/v	1.2 ± 0.4	1.2 ± 0.3	0.97	0.33

t: student t- test; U: Mann Whitney U test; Level of significance <0.05.

Table (4): Comparison between patients with and without pulmonary hypertension as regard iPTH and residual urine output:

	No pulmonary hypertension (n= 37) Mean ± SD	Pulmonary hypertension (n= 63) Mean ± SD	(t)	P value
iPTH No. (%)				
- Low	3 (8.1%)	16 (25.4%)	$X^2 = 4.5$	***0.033***
- Normal	20 (54.1%)	20 (31.8%)	$X^2 = 4.8$	***0.02***
- High	14 (37.8%)	27 (42.8%)	$X^2 = 4.7$	***0.03***
Residual urine output	10 (27%)	17 (27%)	$X^2 = 0.0$	0.99

X^2: Chi-square test; Level of significance < 0.05.

Table (5): Comparison between patients with and without pulmonary hypertension as regard ECHO parameters:

	No pulmonary hypertension (n= 37) Mean ± SD	Pulmonary hypertension (n= 63) Mean ± SD	(t)	P value
Left ventricular Mass index	271.4 ± 71.1	288 ± 68.2	-1.16	0.3
Ejection fraction	55.3 ± 5.5	56.2 ± 6.06	-0.75	0.45
Tricuspid annular plane systolic excursion	19.6 ± 2.6	20.2 ± 3.1	-0.88	0.37
Right atrium size	35.5 ± 4.1	36 ± 4.4	-0.6	0.54
Right ventricle size	42.9 ± 4.6	43.8 ± 5.1	-0.79	0.43
Cardiac output	6.2 ± 1.6	5.4 ± 1.5	-2.3	***0.018***
Tricuspid regurgitant velocity	1.9 ± 0.4	3.6 ± 1.8	-2.1	***0.03***
Pulmonary vascular resistance	2.5 ± 0.9	2.8 ± 0.7	-1.4	0.15
Pulmonary artery pressure	25.03 ± 8.07	53.8 ± 12.7	-12.4	***< 0.001***
A- v fistula flow volume	1166.6 ± 460.6	1079.6 ± 418.2	0.97	0.34

t: student t- test; Level of significance < 0.05.

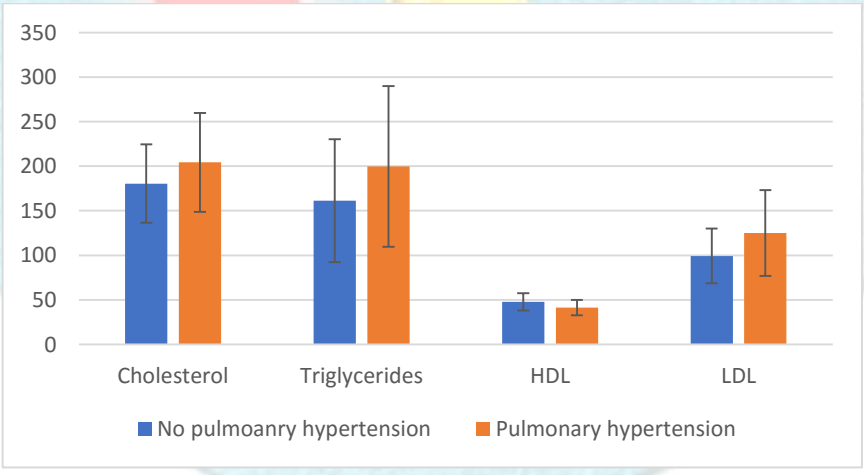

Figure (1): Differences in lipid profile between both groups

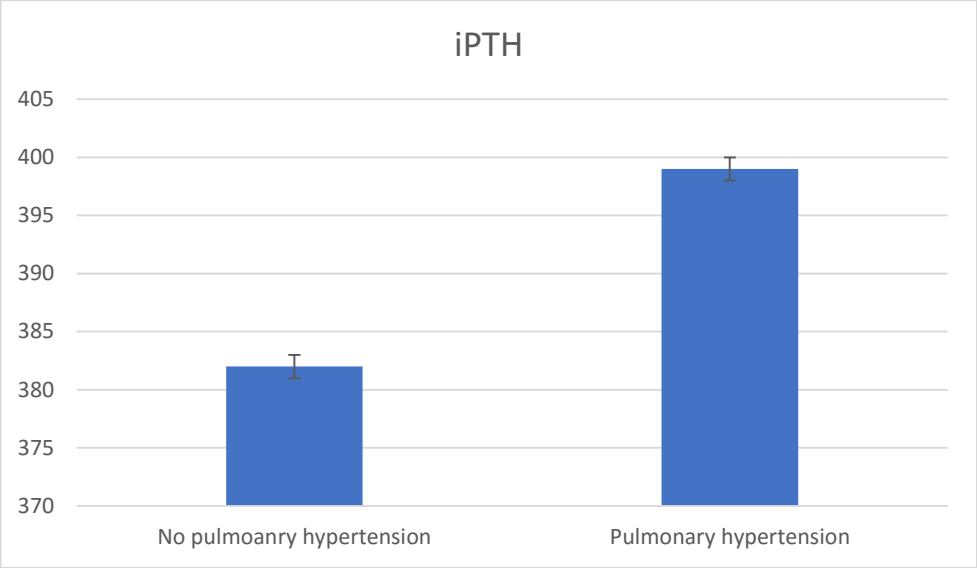

Figure (2): Differences in median value of iPTH between both groups

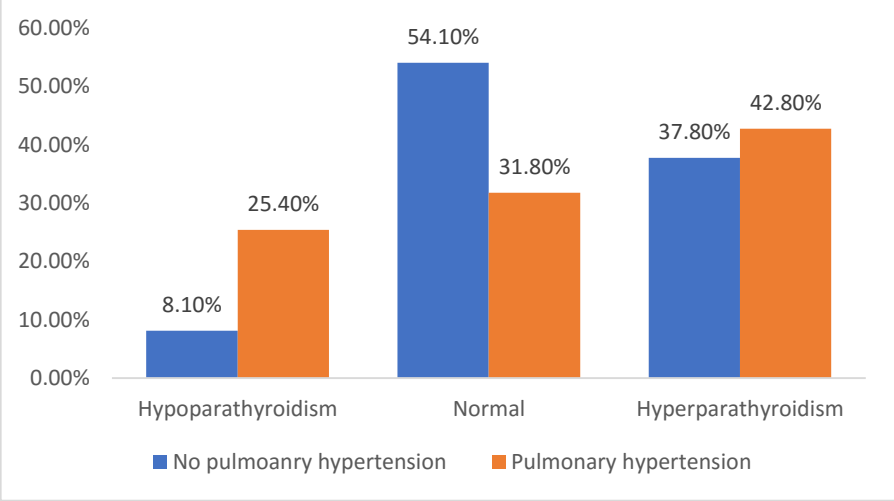

Figure (3): Differences between both groups as regard iPTH status

DISCUSSION

Pulmonary hypertension (PH) is commonly found in pre-dialysis and dialysis-dependent populations, however it is frequently disregarded. The condition leads to impaired functioning of the endothelium, leading to the development of vascular lesions. Oxidative stress and inflammation, resulting from malnutrition, chronic volume overload, and autonomic dysfunction, are factors that lead to endothelial dysfunction and cardiac dysfunction **(Tudoran et al., 2020).**

Hyperparathyroidism, a significant hemodialysis complications, disrupts calcium and phosphorus dynamics, leading to mineral-bone disease, bone metabolism issues, and increased risk of vascular calcification and cardiovascular complications **(Levy et al., 2020)**.

Previous studies evaluated the hyperparathyroidism as a risk factor for pulmonary hypertension through its impact on vascular calcification and remodelling. However, the results showed large

controversy. Thus, this study was conducted to assess the relation between hyperparathyroidism and pulmonary hypertension among hemodialysis patients.

In the present study, about 49% of patients were hypertensives. Hypertension incidence was comparable between patients with and without pulmonary hypertension (p= 0.19). In agreement with the present study, **Ramirez Marmolejo et al. (2020)** found that hypertension was present in 75% of patients. Unlike the present study, **Anandan et al. (2022)** conducted a study on 50 patients and showed that elevated diastolic blood pressure is a significant risk factor for development of pulmonary hypertension among CKD and hemodialysis patients.

The included patients received hemodialysis for about 3.1 ± 1.5 years. Hemodialysis vintage did not differ significantly between patients with and without pulmonary hypertension (p = 0.22). In concordance with the present study, **Zhang et al. (2020)** could not find significant differences between patients with and without pulmonary hypertension as regard dialysis vintage.

In discordance with the present study, **Rroji et al. (2021)** included 125 patients who were receiving haemodialysis for longer duration than that for the included patients in the current study. Unlike the current study, he reported that pulmonary hypertension patients were maintained on haemodialysis for longer duration than non- pulmonary hypertension patients (5 ± 1.5 vs. 3.9 ± 0.6; p= 0.03).

In this study, mean average ultrafiltration rate was 3.3 ± 1.5 L and there were no significant differences between patients with and without pulmonary hypertension as regard ultrafiltration rate. In hand with the present study, **Nagaraju et al. (2021)** did not show significant differences between patients with and without pulmonary hypertension as regard ultrafiltration rate. Similalry, **Engole et al. (2020)** failed to find significant differences between patients with and without pulmonary hypertension as regard ultrafiltration rate.

According to the present study, about 27% of patients had residual renal function with no significant effect on incidence of pulmonary hypertension. In agreement with the present study, **Nagaraju et al. (2021)** did not find significant effect of residual urine on incidence of pulmonary hypertension among hemodialysis patients.

The impact of arteriovenous fistula (AVF) on the development of pulmonary hypertension (PH) in hemodialysis patients is contingent upon the specific type of AVF, the duration of its usage, and the blood flow rates across the AVF. The likely cause of this is an increase in cardiac output (CO), which leads to higher pressures in the pulmonary artery. However, the connection between these factors has not been confirmed yet **(Afzal et al., 2018)**. Thus, we evaluated the effect of AVF and AVF flow volume on incidence of pulmonary hypertension among hemodialysis patients.

Most of included patients received hemodialysis via A- v fistula (96%) and the majority had one AVF (89%) while 7% of patients had 2 AVF. Number of A- v fistula was considered a significant predictor for pulmonary hypertension (p= 0.47). Mean A- v fistula flow volume was 1111.7 ± 434.1 and it did not differ significantly between patients with and without pulmonary hypertension. In agreement with the present study, **Ramirez Marmolejo et al. (2020)** found that 94% of hemodialysis patients who were

included in his study received HD via AVF. On contrary to the present study, **Tudoran et al. (2020)** found that patients with pulmonary hypertension had higher AVF flow volume (median: 1150) than no pulmonary hypertension patients (median: 980) with significant difference ($p< 0.001$).

The commonest cause of ESRD in the present study was hypertension (65%) followed by analgesic nephropathy (11%) and diabetes (9%). In hand with the present study, **Havoshki et al. (2020)** reported hypertension as the most frequent cause of ESRD followed by diabetes. This finding was in concordance to the findings of a previous study in the same province that reported hypertension and diabetes as the most common aetiologies of CKD in 2404 HD patients **(Morovatdar et al., 2019)**. On the other hand, **Zhang et al. (2018)** showed that glomerulonephritis was the most reported cause for ESRD among the included patients in his study (56%) followed by autosomal dominant polycystic kidney disease (55%).

According to the present study, mean hemoglobin levels was 10.7 ± 1.7 g/dL and CBC criteria did not differ significantly between patients with and without pulmonary hypertension. In concordance with the present study, **Havoshki et al. (2020)** demonstrated similar mean values for hemoglobin among included patients in his study and did not show presence of significant differences between patients with and without pulmonary hypertension as regard hemoglobin levels. In discordance with the present study, **Tudoran et al. (2020)** showed that pulmonary hypertension patients had significantly lower mean values for hemoglobin than pulmonary hypertension patients ($p< 0.001$).

In the current study, INR was prolonged significantly in patients with pulmonary hypertension (pulmonary hypertension vs. no pulmonary hypertension: 1.05 ± 0.09 vs. 1.02 ± 0.03; $p= 0.01$). The elevated INR among pulmonary hypertension patients in the present study had an explanation as higher percent of patients in pulmonary hypertension group were maintained on Warfarin. In concordance with the present study, **Zhang et al. (2018)** showed that 19.3% of patients included in his study were maintained on Warfarin in pulmonary hypertension group causing significantly prolonged INR level in this group. On contrary, **Wang et al. (2022)** could not find significant differences in INR between hemodialysis patients with and without pulmonary hypertension.

According to the present study, mean ESR was 41.9 ± 18.5 m/hour. ESR did not differ significantly between patients with and without pulmonary hypertension. In concordance with the present study, **Nagaraju et al. (2021)** did not show presence of significant differences between HD patients with and without pulmonary hypertension as regard ESR. **Wang et al. (2022)** in another study on 137 patients did not show that ESR differed significantly between hemodialysis patients with and without pulmonary hypertension.

The current results showed that mean CRP was 32.8 ± 16.01 and did not differ significantly between patients with and without pulmonary hypertension. In concordance with the current study, **Engole et al. (2020)** did not find presence of significant difference between patients with and without pulmonary hypertension as regard CRP. On contrary, **Rroji et al. (2021)** found that CRP among included hemodialysis patients in his study was 7.3 ± 4.4 and CRP was significantly elevated among pulmonary hypertension patients ($p< 0.001$).

Mean albumin levels of the included patients were 4.1 ± 0.5 g/dL. Albumin was not considered significant predictor for pulmonary hypertension with comparable mean values between patients with and without pulmonary hypertension. In concordance with the present study, **Havoshki et al. (2020)** found similar mean values for serum albumin (4.3 ± 0.5) and did not find significant differences between HD patients with and without pulmonary hypertension as regard albumin levels. On contrary, **Zhang et al. (2018)** showed that patients with pulmonary hypertension had significantly lower mean values for albumin (3.3 ± 0.4 g/dL) than no pulmonary hypertension patients (3.8 ± 0.3 g/dL) ($p< 0.05$).

The study found that patients with pulmonary hypertension had significantly higher cholesterol and triglyceride levels, decreased HDL, and increased LDL compared to those without pulmonary hypertension, indicating a significant risk factor for pulmonary hypertension. In agreement, **Zhang et al. (2018)** demonstrated that pulmonary hypertension patients had significantly increased levels of cholesterol and triglycerides. Also, **Wang et al. (2022)** showed that LDL was significantly higher among HD patients with pulmonary hypertension than patients without pulmonary hypertension ($p= 0.03$). On contrary, **Engole et al. (2020)** did not show presence of significant differences in lipid profile parameters between patients with and without pulmonary hypertension.

In the current study, mean calcium levels were 9 ± 1 mg/dL and mean phosphate level was 6.2 ± 2 mg/dL. Calcium and phosphate levels did not differ significantly between patients with and without pulmonary hypertension. **Havoshki et al. (2020)** found no significant differences in calcium and phosphate levels between HD patients with and without pulmonary hypertension, but the current study found lower mean values. **Tudoran et al. (2020)** found lower calcium levels in pulmonary hypertension patients compared to those without, but no significant differences in phosphate levels were found.

The study found that patients with pulmonary hypertension had significantly elevated mean iPTH, with higher rates of hyperthyroidism and hypoparathyroidism. Patients without pulmonary hypertension had normal PTH, while those with hypertension had hypoparathyroidism. The results suggest that abnormalities in iPTH are associated with increased PAP.In agreement with the present study, **Mortazavi Moghaddam et al. (2020)** showed in his study on 114 patients that iPTH level was 395.67 ± 332 in pulmonary hypertension group and it was significantly higher than that for patients without pulmonary hypertension (275.12 ± 218.44) ($p= 0.03$).

PTH has been linked to toxic vascular effects, potentially causing endothelial dysfunction and increasing serum levels of endothelin-1 and IL-6 **(Jorde et al., 2005)**. PTH stimulates vascular smooth muscle cells to produce collagen and beta-1 integrin, remodeling peripheral vasculature and increasing renin release, leading to enhanced resistance and decreased compliance **(Pascale et al., 2018)**. PH increases pulmonary vascular resistance (PVR) through narrowing of small arteries and arterioles, while decreasing compliance affects the entire vasculature **(Marsh et al., 2018)**. On contrary, **Havoshki et al. (2020)** did not find significant differences between patients with and without pulmonary hypertension as regard iPTH levels.

The study found a mean vitamin D level of 19.1 ± 9.2 ng/dL, which did not significantly differ between patients with and without pulmonary hypertension, **Havoshki et al. (2020)** found no significant differences in vitamin D levels between HD patients with and without pulmonary hypertension, with higher mean values.

Dialysis adequacy, as measured by urea reduction ratio and Kt/v, did not significantly predict pulmonary hypertension incidence among dialysis patients, regardless of their pulmonary hypertension status. **Rroji et al. (2021)** study found no significant impact of hemodialysis adequacy on pulmonary hypertension incidence or significant differences between HD patients with and without PH.

Echocardiography was performed on all participants, and the mean left ventricular mass was 281.9 ± 70, with no significant differences between patients with and without pulmonary hypertension. **Tudoran et al. (2020)** found no significant differences in LVM between patients with and without PH.

The study revealed that there were no notable disparities in ejection fraction between patients with and without pulmonary hypertension. However, it was observed that patients with PH had a significantly diminished cardiac output in comparison to those with normal pulmonary artery pressure.In a similar vein, **Havoshki et al. (2020)** observed no substantial disparities in ejection fraction between individuals with and without pulmonary hypertension. In contrast, **Mortazavi Moghaddam et al. (2020)** discovered that individuals with pulmonary hypertension exhibited a notably reduced ejection fraction in comparison to those without heart disease.

Magder (2021) suggested that reduced ejection fraction in pulmonary hypertension patients is primarily due to passive backward transmission of raised left-sided filling pressures due to systolic or diastolic LV dysfunction. They found that pulmonary hypertension patients showed a significant decrease in cardiac output, despite most patients having homogeneous ejection fraction mean values.

Echocardiographic imaging showed no significant differences in right ventricular function, atrium size, or ventricle size between patients with and without pulmonary hypertension. In concordance with our study, **Rroji et al. (2021)** did not find significant differences between patients with and without PH regarding right atrial volume. Unlike the present study, **Tudoran et al. (2020)** found that TAPSE values were lower in hemodialysis patients and higher in pulmonary hypertension patients, with right atrium and right ventricle diameters.

The study found that TR velocity significantly increased in pulmonary hypertension patients compared to normal PAP patients, indicating right-side affection. In agreement with the present study, **Tudoran et al. (2020) and Rroji et al. (2021)** showed similarly that TR velocity was significantly elevated in PH patients.

In early-stage pulmonary hypertension the right ventricle adapts to afterload, but in advanced stages of pulmonary hypertension, right ventricle systolic function fails, leading to dilatation and RV failure (**Di Lullo et al., 2013 and Naeije and Manes, 2014)**.

The study found that pulmonary hypertension patients had significantly higher arterial blood pressure than those without hypertension, but no significant differences were found in pulmonary vascular

resistance. In agreement with the present study, **Rroji et al. (2021)** showed that pulmonary hypertension patients had significantly elevated PAP than patients with normal PAP ($p< 0.001$). Unlike the present study, they demonstrated that pulmonary hypertension patients had significantly higher pulmonary vascular resistance.

The study focused on parathyroid and vascular calcification, but did not include other markers. Most patients were over 50, a weak point. Larger randomized trials are needed to evaluate medications and long-term effects on hemodialysis patients' morbidity and mortality.

CONCLUSION

Haemodialysis patients are found to be at increased risk for affecting by pulmonary hypertension. In current study, pulmonary hypertension rate was 63%. Multiple risk factors were shown to be incorporated in etiological pathogenesis occurance of pulmonary hypertension among haemodialysis patients. Mineral-bone disease is a common complication of haemodialysis and associated with significant disturbance in calcium and phosphorus homeostasis which by turn had negative impact on vascular calcification. Disturbance in parathyroid release significantly affected incidence of pulmonary hypertension. Hyperparathyroidism had higher rate among pulmonary hypertension patients. The unique finding of the present study that hypoparathyroidism also is associated with increased incidence rate of pulmonary hypertension.

Echocardiographic imaging of haemodialysis patients with pulmonary hypertension revealed presence of significant decreased cardiac output and significant elevated tricuspid regurge velocity when compared to haemodialysis patients who have normal pulmonary artery pressure.

RECOMMENDATIONS

We recommend screening haemodialysis patients for incidence of PH and assessing parathyroid status among haemodialysis patients with pulmonary hypertension. Good control of parathyroid disorders could have a protective and curative role against pulmonary hypertension among haemodialysis patients.

Further randomized trial studies are recommended to assess the effect of treating hyperparathyroidism on regression or prevention of pulmonary hypertension among haemodialysis patients.

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