Pulmonary hypertension in patients with end-stage renal disease under regular hemodialysis: a cross-sectional study

Mohamed F. Abdelghany[a], Walaa H. Mohamad[b], Ahmad B. Elden[c]

[a]Department of Chest Diseases and Tuberculosis, [b]Nephrology Unit, Internal Medicine Department, [c]Critical Care Unit, Internal Medicine Department, Assiut University Hospital, Assiut, Egypt

Correspondence to Mohamed F. Abdelghany, MD. Chest Diseases Assiut University Hospital, Assiut University, PO Box 71111, Assiut, Egypt. Tel: +20 100 680 0525; fax: +20 213 6826; e-mail: mfawzy2013@hotmail.com

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Objectives
We aimed to study the prevalence of each type of pulmonary hypertension (PHT) (precapillary, post capillary and combined) in end stage renal disease patients (ESRD) under haemodialysis (HD). We also studied the correlation between the systolic pulmonary artery pressure (SPAP) and different patient clinical and laboratory variables.

Methods
This cross-sectional study was conducted on 106 HD patients. Demographic and clinical data, blood samples for laboratory variables of the studied patients were all collected. A standard echocardiography was done. Pulmonary function test was performed with standard spirometry.

Results
The total prevalence of PHT in our study population was 77.3%. The prevalence of isolated post capillary PHT, pre capillary PHT and combined pre and post capillary PHT was (32.07%, 23.58% 21.69%) respectively. The prevalence of "unexplained" PHT was 0.9%. There were significant positive correlation between SPAP and smoking index (r=0.427, P=0.035), duration of dialysis (r=0.416, P=0.046), ferrittin level (r=0.312, P=0.048), cardiac output (CO) (r=0.683, P=0.000) and AV fistula flow (r=0.529, P=0.018), while there were significant negative correlation between SPAP and hemoglobin (HB) level (r=−0.598, P=0.010) and serum iron (r=−0.572, P=0.049). Multivariate analysis showed significant association with smoking index (P=0.01), duration of dialysis (P=0.032), HB level (P=0.042) and CO (P=0.000) after adjusting other factors.

Conclusions
In our study there was a high prevalence of PHT in HD patients with a very low prevalence of the unexplained types of PHT. Smoking index, duration of dialysis, HB level and CO were independent risk factors of increased SPAP.

Keywords:
hemodynamic types of PHT, hemodialysis, pulmonary hypertension

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Introduction

Pulmonary hypertension (PHT) is an independent predictor of all-cause mortality in end-stage renal disease (ESRD) patients [1]. Echocardiography is a safe, noninvasive, cost-effective, and easy to use tool for the estimation of systolic pulmonary artery pressure (SPAP) compared with right heart catheterization (RHC) [2]. In addition, echocardiography can estimate pulmonary capillary wedge pressure (PCWP) and pulmonary vascular resistance (PVR) by using proven equations comparable with RHC measurements [3,4]. WHO developed a clinical classification of PHT that categorizes multiple clinical conditions into five groups according to their similar clinical presentation, pathological findings, hemodynamic characteristics, and treatment strategy [5]. PHT in chronic kidney disease (CKD)/ESRD patients was included in WHO group 5 named 'unexplained PHT' [5]. The European Society of Cardiology (ESC) developed a more recent condensed hemodynamic grouping system for PHT [6]. Unfortunately, the current estimated prevalence of PHT in haemodialysis (HD) patients is very diverse and ranges from 27 to 58% [7]. The aim of this study was to measure the prevalence of PHT and hemodynamic types in CKD patients under hemodialysis. Also, we aimed to assess clinical and laboratory variables in this group of patients and the correlation between PHT and these variables in these patients.

Patients and methods

This cross-sectional study was carried out on 106 patients under regular HD in the Nephrology Unit

of Assiut University Hospital from January 2016 to December 2016. Written consents were obtained from all the participants. The study was approved by the ethics committee of faculty of medicine in Assiut University.

Demographic, clinical, and laboratory data

Patients' demographic data and medical history including age, sex, comorbid diseases, smoking index (number of cigarettes×number of years), duration of dialysis, and therapeutic history were obtained. BMI was calculated as [weight (kg)/height^2 (m)]. Body surface area was calculated using the following equation: body surface area (m^2)= 0.007184×(height×0.725)×(weight×0.425). Blood pressure of the patients was recorded. Venous blood samples were collected from the studied patients after end of dialysis sessions. Laboratory measurements included serum levels of creatinine, blood urea nitrogen, low-density lipoprotein cholesterol, fasting blood glucose (FBG), and serum levels of calcium, phosphorous, alkaline phosphatase, intact parathyroid hormone, serum iron, ferritin level, total iron-binding capacity, and serum albumin level.

Echocardiographic data

All echocardiograms were performed with an HDI 5000 instrument (Philips Medical Systems, Bothell, Washington, USA) equipped with a broad band harmonic transducer. A standard echocardiography was done based on apical four-chamber and two-chamber views; 2D echocardiograms of the left ventricle (LV) short axis were recorded at three levels: mitral valve, mid-papillary muscle level, and the apex. All echocardiograms were carried out at the Internal Medicine Department Assiut University Hospital. LV dimensions were calculated using 2D-guided M-mode calculations. The mean value of three measurements of the technically best cardiac cycles was taken after each examination. Cardiac output was measured by the following equation: π×(1/2×left ventricular outflow tract (LVOT) diameter)^2×LVOT velocity time integral (VTI)×heart rate (HR). LV diastolic function was calculated using transmitral *E*-wave velocity using pulsed Doppler with a sample size of 0.7 mm just above mitral valve (MV) leaflets tips, septal *e′* wave measured by tissue Doppler with a sample size of 4.0 mm at the level of MV septal annulus and *E*/*e′* velocity ratio. PCWP was estimated from *E*/*e′* velocity ratio using that equation=1.24×(*E*/*e′*)+1.9 (mmHg) (abnormal PCWP cut level was>15 mmHg) [4]. LV-mass was assessed by the area length method. SPAP was estimated using tricuspid valve regurge (TVR) pressure gradient plus right atrial pressure estimated from inferior vena cava diameter and percentage of inspiratory collapse. PVR was estimated by echocardiography using the following equation: PVR=TRV/RVOT VTI×10+0.16 (abnormal PVR cut level was>3 WU) [3].

Doppler ultrasound

Portal vein congestion index (CI) was estimated using the equation=PVA (πr^2/FV) (abnormal CI cut level was≤0.11 m^2/m/s) [8]. Arteriovenous fistula (AVF) flow volume was calculated by the following formula: area×mean velocity×60 [9].

Pulmonary function test

Spirometry (Quark PFTs ergo, P/N Co9035 –12-99; Cosme SrL, Italy) was used to measure forced vital capacity (FVC%), forced expiratory volume in first second (FEV_1%), and FEV_1/FVC ratio. Obstructive lung disease was further classified according to the Global Initiative for Chronic Obstructive Lung Disease [10]. Restrictive lung disease was graded to mild, moderate, and severe and according to ATS guidelines 2005 [11].

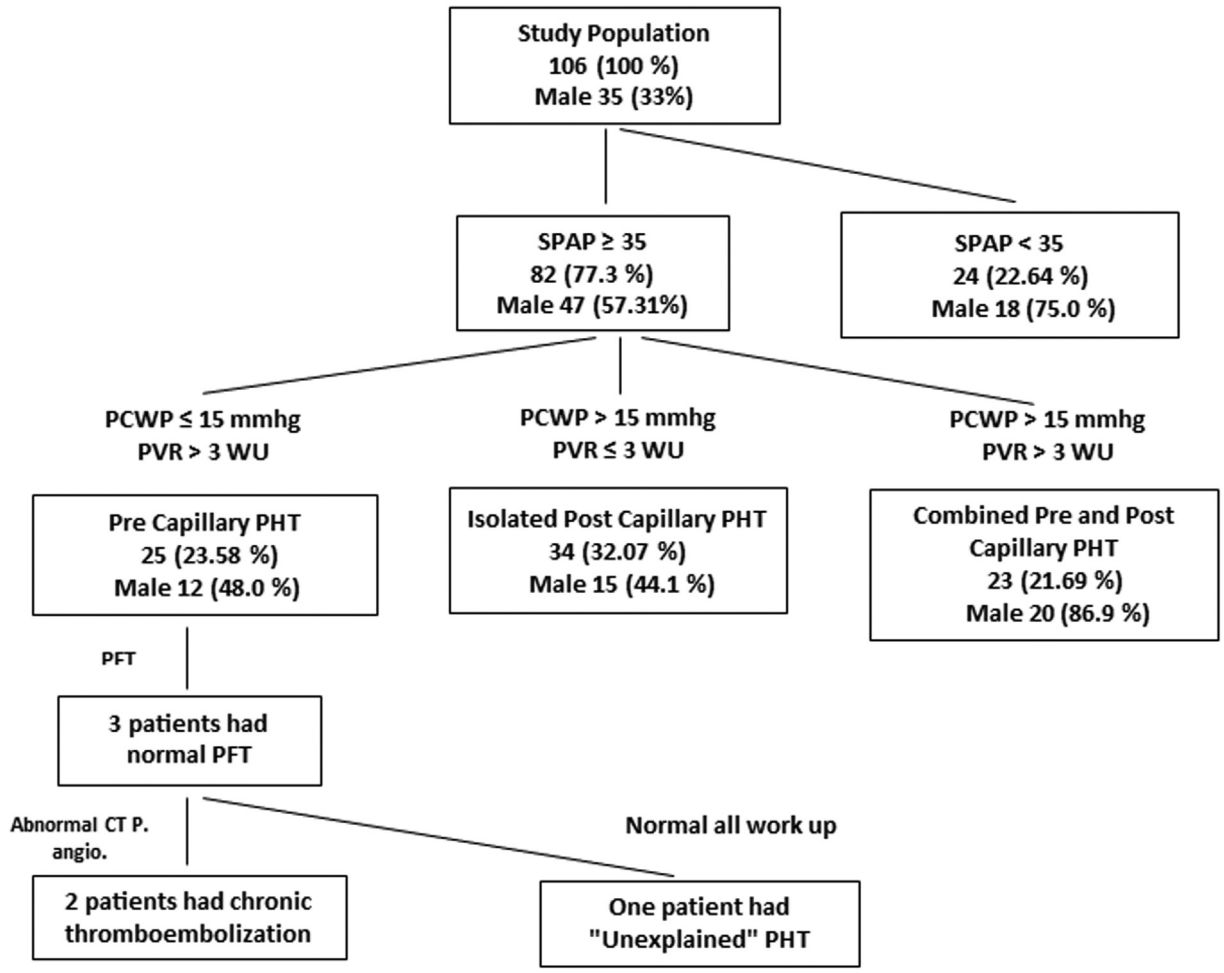
Patient classification

The first parameter of classification was the echocardiographically estimated SPAP with a cut level of at least 35 mmHg. Then, patients with an SPAP of at least 35 mmHg were classified into three hemodynamic groups according to ESC 2015 [6] using estimated PCWP and PVR into: (a) isolated postcapillary PHT, (b) precapillary PHT, and (c) combined precapillary and postcapillary PHT. Three patients with precapillary PHT had normal PFT. These patients had the following investigations done: (a) portal vein CI, (b) HIV serology, (c) immunologic workup (including: ANA abs, anti-ds abs, anti Scl 70 abs, anti-phospholipids abs, anti-bilharzial abs), and (d) mutidetectot computed tomography (MDCT) pulmonary angiography. Two patients had chronic pulmonary thromboembolization and the third one had 'unexplained' PHT (Figure 1).

Statistical analysis

The statistical analysis was performed using SPSS (version 19.0; SPSS Inc., Chicago, Illinois, USA). The Kolmogorov–Smirnov test was used to test normality. Continuous variables were presented as the mean±SD and categorical variables were presented as percentages. Mann–Whitney test was used to compare quantitative variables between groups. Spearman's correlation was used to measure the correlation among qualitative variables. Pearson

Figure 1



Classification of patients according to systolic pulmonary artery pressure (SPAP) and pulmonary capillary wedge pressure (PCWP). PHT, pulmonary hypertension.

correlation was used to measure the correlation among quantitative variables. Multivariate regression analysis was used to test the association between SPAP and smoking index, duration of dialysis, hemoglobin (HB) level, and CO. A *P* value less than 0.05 was considered statistically significant.

Results

Demographic, clinical, laboratory data, and echocardiographic data of the study population are shown in (Tables 1 and 2).

Pulmonary function test of precapillary and combined precapillary and postcapillary PHT patients are displayed in (Table 3).

Abnormal PFT was detected in 54.87% of the precapillary PHT group. About 21.95% had obstructive pattern with a mean smoking index of 743±23.54 (subgroup data not shown in Table 1), while 32.92% had restrictive pattern. high resolution computed tomography (HRCT) chest of patients with restrictive pattern showed a diagnosis of idiopathic pulmonary fibrosis in 10 patients, hypersensitivity pneumonitis in 4 patients, and sarcoidosis in 2 patients. Moreover, all patients with obstructive pattern were diagnosed as chronic obstructive pulmonary disease based on Global Initiative for Chronic Obstructive Lung Disease criteria.

Table 4 presented the association between SPAP and study populations' variables. There were significant positive correlation between SPAP and smoking index (r=0.427, P=0.035), duration of dialysis (r=0.416, P=0.046), ferritin level (r=0.312, P=0.048), cardiac output (r=0.683, P=0.000), and AVF flow (r=0.529, P=0.018), while a significant negative correlation was found between SPAP and HB level (r=−0.598, P=0.010) and serum iron (r=−0.572, P=0.049).

Our regression models R^2 was 90.47% which explain most of SPAP changes. SPAP changes were

Table 1 Demographic and laboratory data of all studied patients

Variables	Mean±SD
Age (years)	46.60±15.33
BMI (kg/m^2)	25.41±4.43
BSA (m^2)	1.71±0.48
DM	45 (51.2)
HTN	57 (65.1)
Smoking index	635±132.1
Duration of dialysis (year)	6.54±4.37
SBP (mmHg)	154.34±15.33
Blood urea (mg/dl)	50.42±19.70
Serum creatinine (mg/dl)	7.82±1.16
FBG (mg/dl)	222±23.31
iPTH (pg/ml)	282.31±328.45
ALP (U/l)	162.43±129.59
LDL-C (mg/dl)	155.35±65
HB level (g/dl)	10.54±1.56
Serum iron (mg/dl)	143.98±37.97
Ferritin (ng/ml)	4049.22±1887.82
TIBC (mg/dl)	215.15±39.24

Values are expressed as mean±SD and *n* (%). ALP, alkaline phosphatase; BSA, body surface area; DM, diabetes mellitus; FBG, fasting blood glucose; HB, hemoglobin; HTN, hypertension; iPTH, intact parathormone; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TIBC, total iron-binding capacity.

Table 2 Echocardiographic parameters of all studied patients

Variables	Mean±SD
LVEF (%)	56.85±11.06
LV-mass index (g/m^2)	232±44
E (m/s)	0.96±0.25
e′ (m/s)	0.10±0.04
E/*e′*	11.27±4.97
PASP (mmHg)	55.48±15.23
Cardiac output (l/min)	5.34±0.62
AVF flow (ml/min)	548.48±43.82

Values are expressed as mean±SD. AVF, arteriovenous fistula; LA, left atrium; LV, left ventricle; SPAP, systolic pulmonary artery pressure.

Table 3 Pulmonary function test of precapillary pulmonary hypertension and combined precapillary and postcapillary pulmonary hypertension

Pulmonary function	Precapillary PHT: 25 (23.58%) [*n* (%)]	Combined precapillary and postcapillary PHT: 23 (21.69%) [*n* (%)]
Normal	3 (12.0)	0
Obstructive pattern	6 (24.0)	12 (52.1)
Restrictive pattern	16 (64.0)	11 (47.8)

PHT, pulmonary hypertension.

significantly associated with smoking index, duration of dialysis, HB level, and CO (Table 5).

On comparison between HD patient with PHT (SPAP≥35) and patients without PHT, the hypertensive group had a significantly higher smoking index, systolic blood pressure, and FBG.

Moreover, HD patients with isolated postcapillary PHT had a significantly higher prevalence of hypertension and diabetes mellitus, higher level of FBG and low-density lipoprotein cholesterol.

Also, the group of patients with combined precapillary and postcapillary PHT had a significantly higher level of serum creatinine, a higher prevalence of hypertension and diabetes mellitus, and a higher level of FBG than other groups of patients (Table 6).

The prevalence of each type of PHT is shown in (Figure 1). The total prevalence of PHT in our study population was 77.3%. Moreover, the prevalence of isolated postcapillary PHT was 32.07%, while the

Table 4 Correlation between systolic pulmonary artery pressure and other patients' characteristics

Patients characteristics	SPAP	
	r value	*P* value
Age (years)	0.281	0.217
HTN	0.193	0.392
DM	0.148	0.094
Smoking index	0.427	**0.035***
Duration of dialysis (years)	0.416	**0.046***
SBP (mmHg)	0.183	0.603
FBG (mg/dl)	0.252	0.105
Blood urea (mg/dl)	0.270	0.173
Serum creatinine (mg/dl)	0.202	0.312
iPTH (pg/ml)	–0.099	0.400
LDL (mg/dl)	–0.319	0.496
ALP (U/l)	0.053	0.666
HB (g/dl)	–0.598	**0.010***
Serum iron (mg/dl)	–0.572	**0.049***
Ferritin (ng/ml)	0.312	**0.048***
TIBC (mg/dl)	0.323	0.060
CO	0.683	**0.000**
AVF	0.529	**0.018**

ALP, alkaline phosphatase; AVF, arteriovenous fistula; DM, diabetes mellitus; FBG, fasting blood glucose; HB, hemoglobin; HTN, hypertension; iPTH, intact parathormone; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; TIBC, total iron-binding capacity. **P*-value is significant at 0.05.

Table 5 Multivariate analysis of factors affecting systolic pulmonary artery pressure

Model	Standard coefficients	*t* value	*P* value
Smoking index	0.649	8.341	*0.01**
Duration of dialysis (year)	0.573	5.105	*0.032**
HB (g/dl)	0.352	4.536	*0.042**
CO	0.638	10.37	*0.000**

HB, hemoglobin. **P*-value is significant at 0.05.

Table 6 Comparison between hemodynamic pulmonary hypertension subgroups and patients' laboratory and cardiac parameters

	Normal SPAP	Isolated postcapillary PHT	Precapillary PHT	Combined precapillary and postcapillary PHT
Age (years)	44.46±14.73	43.94±17.23	39.71±10.85	44.33±8.96
	[1]*P*=0.215	[2]*P*=0.328	[3]*P*=1.000	[4]*P*=0.486
HTN (%)	45.87	89.95	27.34	78.48
	P=0.222	*P*=0.000	*P*=0.561	*P*=0.001
DM (%)	67.34	90.56	20.71	80.67
	P=0.119	*P*=0.002	*P*=0.102	*P*=0.000
Smoking index	202.56±34.29	863.54±235.56	1025±34.65	928.56±83.94
	P=0.000	*P*=0.078	*P*=0.298	*P*=0.195
Duration of duration (years)	7.81±3.71	6.48±2.61	7.67±3.94	8.33±4.93
	P=0.881	*P*=0.411	*P*=0.600	*P*=0.445
SBP (mmHg)	116.45±5.56	150.19±18.35	140.04±16.55	132.52±12.72
	P=0.028	*P*=0.451	*P*=0.184	*P*=0.156
FBG (mg/dl)	101.38±4.34	168.39±18.39	117.48±1.49	155.67±12.87
	P=0.000	*P*=0.001	*P*=0.451	*P*=0.002
Blood urea (mg/dl)	136.50±47.26	149.92±46.73	142.38±41.78	177.50±34.65
	P=0.865	*P*=0.828	*P*=0.497	*P*=0.296
Serum creatinine (mg/dl)	7.68±1.96	7.42±1.54	7.76±0.99	12.45±1.63
	P=0.497	*P*=0.587	*P*=0.027	*P*=0.037
iPTH (pg/ml)	245.19±302.62	227.41±308.71	353.58±436.43	376.00±294.95
	P=0.370	*P*=0.271	*P*=0.161	*P*=0.396
LDL-C (mg/dl)	144.34±10.93	156.38±12.89	120.61±12.67	120.45±12.73
	P=0.065	*P*=0.042	*P*=0.029	*P*=0.985
HB (g/dl)	11.25±0.94	9.49±1.19	10.28±1.69	10.03±1.01
	P=0.398	*P*=0.385	*P*=0.380	*P*=0.599
Serum iron (mg/dl)	150.10±40.57	121.92±56.43	158.27±62.53	147.00±137.18
	P=0.522	*P*=0.148	*P*=0.850	*P*=0.290
Ferritin (ng/ml)	3472.87 ±2629.71	3940.44±2884.27	4082.91 ±3206.73	3360.50±2683.47
	P=0.018	*P*=0.310	*P*=0.584	*P*=0.844
TIBC (mg/dl)	207.20±74.91	196.25±34.04	237.91±69.49	229.50±33.23
	P=0.205	*P*=0.166	*P*=0.201	*P*=0.844
Cardiac output (l/min)	4.49±0.94	4.54±0.52	6.52±0.88	6.31±0.62
	P=0.437	*P*=0.000	*P*=0.000	*P*=0.451
AVF flow (ml/min)	563.32±95.01	588.41±89.52	582.48±43.82	579.48±53.82
	P=0.492	*P*=0.916	*P*=152	*P*=0.825

AVF, arteriovenous fistula; DM, diabetes mellitus; FBG, fasting blood Glucose; HB, hemoglobin; HTN, hypertension; iPTH, intact parathormone; LDL-C, low-density lipoprotein cholesterol; PHT, pulmonary hypertension; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; TIBC, total iron-binding capacity. [1]*P*: compression between normal SPAP and other groups. [2]*P* compression between isolated postcapillary PHT and precapillary PHT. [3]*P*: compression between isolated postcapillary PHT and combined precapillary and postcapillary PHT. [4]*P*: compression between precapillary PHT and combined precapillary and postcapillary PHT.

prevalence of precapillary PHT was 23.58% and the prevalence of combined precapillary and postcapillary PHT was 21.69%. However, 'unexplained' PHT was presented in only one (0.95%) patient.

Discussion

PHT is defined as echocardiographically estimated SPAP of at least 35 mmHg. Previous literature reported PHT in patients with CKD/ESRD with very diverse ranges of prevalence [12]. WHO categorized PHT into five etiological groups. PHT in CKD/ESRD patients was included in the WHO group 5 and was named 'unexplained PHT' [5]. However, CKD/ESRD patients usually have multiple comorbid conditions that can contribute to and explain the development of PHT in this group of patients. So, PHT in CKD/ESRD patients have overlapped WHO grouping. Available data reported a prevalence of PHT in HD patients that range from 27 to 58% [7]. In this study, the total prevalence of PHT is higher than the reported range (77.3%). The higher global prevalence of PHT in our population can be explained by the following:

(1) Bozbas *et al.* [13] stated that PHT prevalence correlates with the comorbid diseases. The high prevalence of LV dysfunction and chronic lung

disease (32.07 and 23.58%), respectively, in our recruit explain our higher prevalence of total PHT.

(2) In this study, the mean age was 46.60±15.33. PHT prevalence correlates with the age of the cohort being studied. In a previous study done on a younger group of CKD patients (mean age 31.6 ±10.2), the overall prevalence of all types of PH was only 17% [13].

(3) The volume status of the patient is known to be one of the factors affecting the degree of PHT. As volume status changes, the estimated PHT may differ at times of assessment [7].

(4) There is evidence that the duration of dialysis has a positive correlation with the development of PHT. The duration of dialysis in our cohort was 6.54 ±4.37 years. In a previous study, the increase in the duration of dialysis from 1 to 2 years increased the prevalence of PHT from 38 to 58% [14]. Also, even after adjusting other factors with multivariate analysis in our study, there was significant positive correlation between SPAP and duration of dialysis.

In this study, the prevalence of 'unexplained' PHT was 0.95%. The elevated PCWP has been emerged as the most important contributor to the 'unexplained' PHT in CKD/ESRD patients [15]. It has been attributed to subclinical LV dysfunction that is not fully captured by routine echocardiogram [16]. The use of E/e' ratio to estimate left-sided filling can unmask the hidden LV dysfunction and the routine use of this tool can change the prevalence of the so-called 'unexplained' PHT in CKD/ESRD patients.

Correlation analysis in this study showed significant negative correlation between SPAP and HB and serum iron levels even after adjusting other factors with multivariate analysis. Multiple studies have found lower HB levels in patients with PHT compared with those without PHT, which has been attributed to the increased preload on the right heart chambers [7,17,18].

In this study, there was a significant positive correlation between SPAP and ferritin level. Serum ferritin is not only an iron index but also an acute phase reactant. A subclinical inflammatory state in ESRD patients can increase serum ferritin level [19]. The low grade inflammation is usually associated with a hyperdynamic state which also increases preload on the right heart chambers and causes an elevation of the SPAP.

A high CO state can cause PHT by increasing RV preload that can worsen by anemia and fluid overload [18]. CO had a significant positive correlation with SPAP even after adjusting other factors with multivariate analysis.

Data about the role of AVF flow mediated CO elevation in the development of PHT is conflicting [20,21]. In this study, despite a positive correlation between AVF flow and SPAP, multivariate analysis did not show a significant relation between them.

By comparing the ESC PHT groups in our population, there was a higher CV risk factors profile in both groups of patients (isolated postcapillary PHT and combined precapillary with postcapillary PHT) compared with isolated precapillary PHT, which signify the burden of these CV risk factors on LV performance and subsequent elevation of PCWP.

Conclusion

In this study, the prevalence of PHT in ESRD patients was 77.3%. PHT in these patients can be classified in one of WHO groups 1 to 4 with thorough investigations. The 'unexplained' PHT accounted for only 0.95% of all PHT cases. Smoking index, duration after dialysis, HB level, and CO were independent risk factors for elevated SPAP. Postcapillary PHT (isolated or combined with precapillary) represented 69.5% of all PHT; this group had a higher CV risk factors profile than patients with either normal or isolated precapillary PHT. About 23.58% were classified as precapillary PHT which denotes the relatively high prevalence of comorbid chest diseases in ESRD patients.

Study limitations and recommendations

SPAP was measured by echocardiography without obtaining direct invasive measurements using RHC. However, echocardiographically estimated SPAP have a good correlation to RVC-driven SPAP in some studies [2]. As the CV risk factors were high in 69.5% of PHT patients (isolated postcapillary PHT and combined precapillary and postcapillary PHT), modification of these risk factors can modify the incidence and prevalence of PHT. We recommend smoke quitting programs to be incorporated in the dialysis units as well as early diagnosis and treatment of comorbid chest diseases. We recommend also treatment of infections if any, and good control of anaemia.

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Conflicts of interest

None declared.

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