Pulmonary Hypertension in a Group of Patients with Various Stages of Renal Disease

Sayf Nasseer Hassan[1], Qais Nemah Raheeem Al-Omary[2], Ahmad Shams Aldeen[3]

[1]Hemodialysis Unit, Ibn Sena Teaching Hospital, Mosul, Iraq, [2]Iraqi Center for Heart Diseases, Baghdad Teaching Hospital, Baghdad, Iraq, [3]Mosul Cardiac Center, Mosul, Iraq

Abstract

Background: The pathogenesis of pulmonary hypertension (PHT) associated with renal failure is complex. It includes metabolic and hormonal changes, high cardiac output due to arteriovenous fistula (AVF), anemia, and other factors. **Objectives:** The objective is to identify PHT frequency and associated factors in patients on hemodialysis (HD) compared to patients, not on HD. **Methods:** A cross-sectional study was conducted at Ibn Sena teaching hospital/Mosul and included 100 diabetic males with end-stage renal disease on HD (Group 1) compared to 96 diabetic males (of similar age) with chronic kidney disease but not on HD (Group 2) to assess the pulmonary artery pressure using Doppler echocardiogram. Patients with other causes of PHT such as heart failure and chronic lung disease were excluded from the study. **Results:** 42 (42%) of patients in Group 1 had PHT and 12 (12.5%) patients in Group 2. There were statistically significant differences between patients with and without PHT regarding ejection fraction (EF), but no significant differences regarding age, duration of dialysis, hemoglobin (Hb), and vascular access type in both groups. **Conclusions:** EF had a relationship with PHT, whereas the duration of dialysis, age of patients, Hb, and dialysis access type had no relationship to PHT. **Recommendations:** More studies are needed in our country regarding PHT in patients with variable stages of renal disease with larger sample sizes and different designs with the inclusion of data and parameters that were missing in our study such as duration of AVF creation.

Keywords: Chronic kidney disease, hemodialysis, pulmonary hypertension

Introduction

Chronic kidney disease (CKD) has stages that are better identified based on the estimation of the glomerular filtration rate (GFR) rather than serum creatinine (S. Cr) concentration. Estimated GFR or eGFR is reported now by many laboratories using one of the equations made for this purpose. Although GFR decreases with increase in human age, its decrement indicates derangement of renal function, with the consequences related to the corresponding stage of CKD. Women have a lower mean GFR than men.[1]

The validity of equations for GFR estimation is guaranteed when the patient is in a steady state, i.e., no decrease or increase in the S. Cr over days. Stages 1 and 2 CKD (GFR ≥90, ≥60 ml/min/1.73 m^2, respectively) are usually not associated with any symptoms arising from GFR decrement. If the decline in GFR progresses to stages 3 and 4 (GFR ≥30, ≥15 ml/min/1.73 m^2, respectively), clinical and laboratory complications of CKD become more prominent. All organ systems can be affected, but some complications are more prominent including anemia; decreased appetite; disturbances in calcium, phosphorus, and mineral-regulating hormones, such as 1,25 (OH) 2D3 (calcitriol), parathyroid hormone, and fibroblast growth factor 23 (FGF-23); and disturbances in sodium, potassium, water, and acid-base homeostasis. Values of eGFR of many patients, especially the elderly, will be compatible with stage 2 or 3 CKD, but no further deterioration in renal function will happen in the majority of these patients. The physicians in primary health care are recommended to recheck the stability of renal function, and if no proteinuria was found, the patient can usually be managed in this setting, however, if there was

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Address for correspondence: Dr. Sayf Nasseer Hassan, Ibn Sena Teaching Hospital, Mosul, Iraq.
E-mail: doctoser75@gmail.com

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GFR decrement, uncontrolled hypertension, or proteinuria, it is better to refer to a nephrologist. When the patient progresses to stage 5 CKD (GFR <15 ml/min/1.73 m^2), toxins accumulate and usually cause disturbance in the water and electrolyte homeostasis and the daily living of patients, and eventually leading to the uremic syndrome.[1]

Cardiovascular disease is a well-recognized and important source of mortality in patients with CKD.[2] Moreover, despite the advanced health care offered during renal replacement treatment (RRT), mortality remains high, indicating the need for better cardiovascular care of CKD patients. Coronary artery disease is not the only form of cardiovascular disease happening in CKD, but other forms are also prevalent.[3] Pulmonary hypertension (PHT) is one form affecting patients undergoing hemodialysis (HD) through the creation of an arteriovenous graft or fistula (AVF) where the pulmonary vascular disease is multifactorial.[4-6]

Regardless of the etiology of PHT, it carries increased morbidity and mortality[7] and has been found recently as a strong independent predictor of mortality in HD patients.[8] PHT is associated with multiple hemodynamic disturbances originating from variable causes. In 1973 the World Health Organization endorsed a conference where a classification of PHT was suggested and was based on two categories (primary and secondary PHT).[9] In 1998, an updated classification established five categories of PHT and supplanted the first classification.[10] Since that time, there were simple modifications on the classification, and in 2008 the last classification maintained 5 categories [Figure 1].[11] In the 2008 classification and in more recent guidelines by the European Society of Cardiology (ESC)[12] for the first time attention was given to PHT in dialysis patients which was classified in the 5th category, i.e., in a category including various forms of PHT with unclear or multifactorial etiology.

Pulmonary artery hypertension (PAH) category I, requires invasive hemodynamic procedures for diagnosis and demands that the mean pulmonary artery pressure (mPAP) be ≥25 mm/Hg, associated with pulmonary vascular resistance >3 Wood units and that pulmonary wedge pressure (PWP) i.e., the left ventricular (LV) filling pressure be ≤15 mm/Hg. High PAH in this case is caused by high vascular resistance at the level of pulmonary arterioles while downstream pressure in the pulmonary veins and the left heart chambers is normal [Figure 2].[13]

The second category identifies PHT caused by systolic or diastolic dysfunction of LV or left-sided mitral and/or aortic valvular disease. In this category, PWP is high (>15 mm/Hg) because the LV disorders elevate the LV pressure which in turn is transmitted back to the atrium, pulmonary veins and the pulmonary artery (PA), i.e., the PA pressure is passively increased due to LV disorder [Figure 2].[13]

The third category includes PHT secondary to diseases of the lung and sleep apnea, the fourth includes PA occlusive diseases

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Figure 1: Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)[11]

caused by thromboembolic phenomena and other occlusive/compressive phenomena and the fifth is the one including PHT in dialysis patients and it includes miscellaneous forms with uncertain etiology.[13]

Echo–Doppler procedures are useful to estimate the systolic PAP (sPAP), a surrogate of mPAP, which is calculation is based on the tricuspid regurgitation jet velocity (TRV). In the absence of PA stenosis, right ventricular systolic pressure (RVSP) approximates sPAP by Echo–Doppler.[14]

sPAP (assumed to be equal to RVSP) can be then estimated by calculating RVSP with the Bernoulli equation formula:

(PAP = 4 x (peak tricuspid regurgitant jet velocity)^2 + estimated right atrial pressure [RAP]) where RAP calculation is based on the diameter of the vena cava and the extent of its inspiratory collapse or by a fixed estimate when inferior vena cava measurements are not available.[14]

Echo–Doppler procedure has a major limitation which is inaccuracy of estimation particularly so when TRV is difficult to visualize, however, Echo–Doppler study remains useful for the PHT screening and the management of patients with PHT.[15]

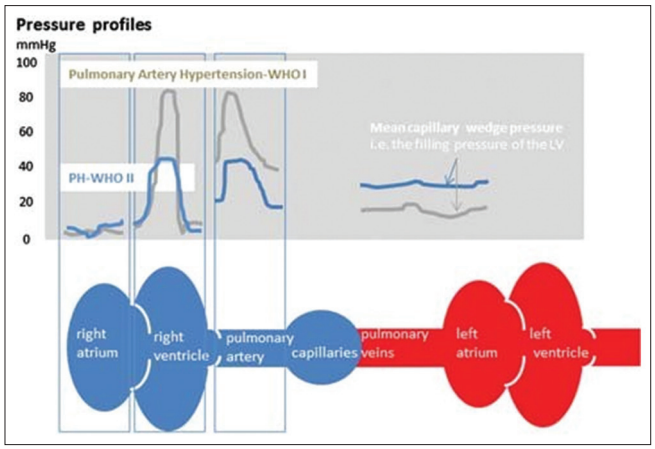

Figure 2: Typical profiles of pressure during right heart catheterization studies of a patient with compensated PAH and a patient with PHT secondary to LV disorders.[13] PAH: Pulmonary artery hypertension, PHT: Pulmonary hypertension, LV: Left ventricular

PHT is defined as sPAP ≥35 mmHg at rest by Doppler echocardiography estimation, and graded into mild, moderate, and severe (>35, >50, >70 mm/Hg, respectively). It has been repeatedly reported in patients with CKD, both predialysis and during regular RRT, with a high but variable prevalence.[16] Multiple factors have been implicated in the presence of this pathology: PA calcifications due to alterations in calcium and phosphate absorption and excretion leading to secondary hyperparathyroidism; and the creation of AVF with its consequent hemodynamic modifications manifested by a reduced ability of pulmonary vessels to accommodate the arteriovenous (AV) access-mediated elevated cardiac output, possibly due to derangement in the metabolism of nitric oxide–endothelin, but there still no complete explanation of this pathogenesis. Furthermore, procedures such as access thrombectomy may predispose to small pulmonary emboli causing elevated pulmonary pressure.[17,18]

This study aimed to identify the PHT frequency in patients on maintenance HD therapy compared to patients with CKD but not on HD and looking for a possible relationship between the presence of PHT and the age of the patients (in both groups) or duration of dialysis (in Group 1) or some of the metabolic parameters included in the study (in both groups).

Methods

From January 2018 to march 2019, two groups of patients were included in our study, Group 1 included 100 patients with ESRD on HD, Group 2 included 96 patients with stage 4 and 5 CKD but not on HD. The age of patients ranged from 18 to 80 years. The equation used to estimate GFR is from The Modification of Diet in Renal Disease study (Estimated GFR ml/min/1.73 m2) = 1.86 × (S. Cr) − 1.154 × (age) − 0.203).

Patients in Group 1 were on HD for more than 1 month via surgically created native AVF or central venous catheter (CVC). They were dialyzed two times per week at dialysis unit of Ibn-Sena teaching hospital/Mosul city. In both groups, the patients were diabetic males and accepted to undergo echocardiography.

We excluded patients with any comorbid conditions predisposing to secondary PHT like cardiac disease, pulmonary disease, collagen-vascular disease, excessive smoking and patients with body mass index more than 35 or <18 kg/m^2 (Through history taking, physical examination, and investigations).

The following demographic and clinical data relevant to the study were obtained from patients' files: age, duration of dialysis treatment, smoking, and the increase in weight during the interdialytic time (interdialytic weight gain). The mean dry weight of each patient was averaged from the values recorded at the end of the dialysis sessions during the same period. Hemoglobin (Hb) and hematocrit were measured by machine centurion (centurion company/united kingdom) at least two times during the study. Serum albumin (S. albumin) level was also measured by machine BT1500 in the laboratory unit of Ibn Sena teaching hospital.

sPAP was estimated by Doppler echocardiography. A two-dimensional and M mode doppler echocardiography was performed by the machine (Philips En visor c/united medical instruments) at Ibn Sena teaching hospital to all patients after 24 h from the completion of dialysis to ensure that the patient had reached the dry weight which is clinically determined by nephrologist to avoid clinically evident volume overload. A tricuspid regurgitation systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler echocardiographic probe. PHT was defined as an sPAP ≥35 mm/Hg, and the RVSP was calculated from the modified Bernoulli equation, in which the estimated RAP was estimated to be 10 mm/Hg.

The PHT frequency was calculated for both groups and was compared against the demographic and the clinical variables in both groups using the *t*-test and the Chi-square test as appropriate. Excel 2010 statistical program was used. Values of the continuous variables were expressed as mean ± standard deviation (SD). $P \leq 0.05$ was considered statistically significant.

The study was conducted in accordance with the ethical principles that have their origin in the declaration of Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

Results

The mean ± SD of age (in years) in Group 1 and Group 2 was 51.1 ± 16.62 and 65.8 ± 11.26, respectively, with a statistically significant difference between them ($P < 0.001$). The mean ± SD of the duration of dialysis (in months) for Group 1 was 10.7 ± 7.34. The mean ejection fraction (EF) ± SD in Group 1 and Group 2 was 55.0 ± 1.74 and 55.9 ± 2.35,

respectively, with a statistically significant difference between them ($P = 0.003$). The Mean Hb ± SD in Group 1 and Group 2 was 9.4 ± 1.54 g/dl and 10.0 ± 1.94 g/dl, respectively, and there was no statistically significant difference between them. Mean S. albumin ± SD in Group 1 and Group 2 was 34.2 ± 2.80 g/dl and 32.8 ± 4.42 g/dl, respectively, and there was no statistically significant difference between them. These results are shown in Table 1.

PHT was observed in 42 (42%) of patients in Group 1 and 12 (12.5%) of patients in Group 2 and there was a statistically significant difference between frequencies of patients with and without PHT depending on the group they belong to. These results are shown in Figure 3.

sPAP in Group 1 and Group 2 was 51.7 ± 6.4 mm/Hg and 48.3 ± 8.2 mm/Hg, respectively, with a statistically significant difference between them ($P = 0.001$). These results are shown in Figure 4.

Comparison of mean of age ± SD of patients with and without PHT in Group 1 and Group 2 showed no statistically significant difference regarding the presence of PHT in both groups. These results are shown in Table 2.

Regarding the duration of dialysis, in Group 1, no statistically significant difference was found between it and the grades of PHT (among the 42 patients within Group 1 who have PHT).

The cutoff point of the duration of dialysis was 6 months. These results are shown in Table 3.

Furthermore, no significant difference was found between the duration of dialysis and the presence of PHT (among the 100 patients of Group 1). This result is shown in Table 4.

In Group 1, the mean ± SD of EF of patients with and without PHT was 53.0 ± 1.02 and 54.1 ± 2.0, respectively, with a statistically significant difference between them ($P = 0.001$). The Mean ± SD of Hb of patients with and without PHT was 9.7 ± 1.57 and 9.1 ± 1.49, respectively, with no statistically significant difference between them. Mean ± SD of S. albumin of patients with and without PHT was 35.1 ± 1.98 and 33.5 ± 3.11, respectively, with a statistically significant difference between them ($P = 0.004$). In Group 2, the mean ± SD of EF of patients with and without PHT was 54.2 ± 1.09 and 55.4 ± 1.9, respectively, with a statistically significant difference between them ($P = 0.035$). Mean ± SD of Hb of patients with and without PHT was 10.7 ± 2.07 and 9.9 ± 1.92 with no statistically significant difference between them. The Mean ± SD of S. albumin of patients with and without PHT was 34.0 ± 5.22 and 32.6 ± 4.35, respectively, with no statistically significant difference between them. These results are shown in Table 5.

Regarding dialysis access type in Group 1; 86 patients had AVF (of which, 36 [36%] had PHT); whereas 14 patients had CVC line (of which 6 [6%] had PHT). There was no statistically significant difference between frequencies of patients with and without PHT according to dialysis access type. These results are shown in Table 6.

Discussion

Our study found that the prevalence of PHT among patients with CKD stage 4 and 5 was 12% which is within the range of 8%–39% found in other studies.[4,5,19,20] The prevalence of PHT in HD patients was 42% which is close to the result

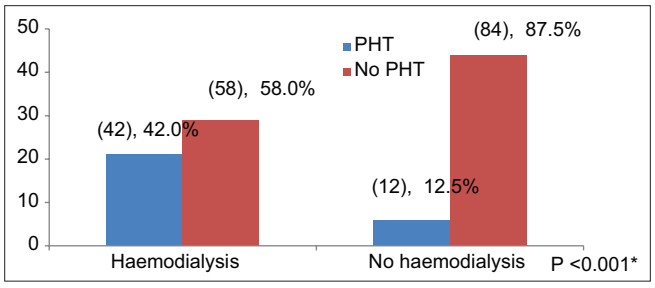

Figure 3: The frequency and percentage of pulmonary hypertension in the study groups

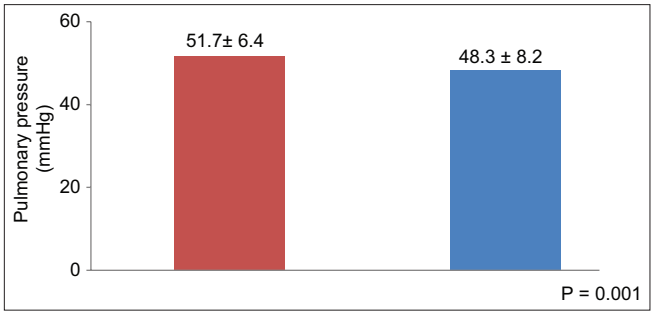

Figure 4: The mean pulmonary pressure in group one (red color) and Group 2 (blue color)

Table 1: Mean age, duration of dialysis, ejection fraction, hemoglobin and serum albumin for patients in Group 1 and Group 2

Parameters mean±SD (with range for some parameters)	Group 1 "Haemodialysis"	Group 2 "No haemodialysis"	*P**
Age (years)	51.1±16.62 (18-73)	65.8±11.26 (28-80)	0.000
Duration of dialysis (months)	10.7±7.34 (1-25)	-	-
EF (%)	55.0±1.74	55.9±2.35	0.003
Hb (g/dL)	9.4±1.54	10.0±1.94	0.105
Serum albumin (g/L)	34.2±2.80	32.8±4.42	0.065

**t*-test was used. EF: Ejection fraction, Hb: Hemoglobin, SD: Standard deviation

Table 2: The relationship between the mean of age of the patients and presence of pulmonary hypertension in the study groups

	Mean age±SD	*P**
Group 1		
PHT (*n*=42)	49.2±11.8	0.35
No PHT (*n*=58)	52.4±19.6	
Group 2		
PHT (*n*=12)	64.8±2.2	0.75
No PHT (*n*=84)	65.9±12.0	

**t*-test was used. PHT: Pulmonary hypertension, SD: Standard deviation

Table 3: The relationship between duration of dialysis and grades of pulmonary hypertension in group one patients (*n*=42)*

Duration of dialysis (months)	Grades of PHT		*P***
	Mild PHT (35-49 mmHg), *n* (%)	Moderate PHT (50-69 mmHg), *n* (%)	
≤6	2 (5)	12 (28)	0.31
≥6	8 (19)	20 (48)	
Total	10 (24)	32 (76)	100%

*No severe PHT was found in group one, **Chi-square test was used, df=1. PHT: Pulmonary hypertension

Table 4: The relationship between duration of dialysis and the presence of pulmonary hypertension in group one (*n*=100)

Duration of dialysis	PHT (*n*=42), *n* (%)	No PHT (*n*=58), *n* (%)	*P**
≤6	12 (12)	26 (26)	0.09
>6	30 (30)	32 (32)	
Total	42 (42)	58 (58)	100%

*Chi-square test was used, df=1. PHT: Pulmonary hypertension

by Nakhoul *et al*.[21] which found it to be 48%, while Yigla *et al*.[17] found it to be 57.1% and Fabbian *et al*.[22] found it to be 58.6%. Several reasons play a role in the variation of these prevalence estimates. First, the timing of performance of echocardiograms which may influence prevalence estimates where the interdialytic increase in volume may increase PAP, for example, Amin *et al*.[6] performed echocardiograms within 4 h after dialysis and found a prevalence of 29%, whereas Fabbian *et al*.[22] performed echocardiograms the day following dialysis and found a prevalence of 58.6%. In our study, echocardiograms were done within 24 h after the HD was completed to possibly avoid the effect of volume overload, which is almost always present immediately before the HD treatment in the schedule of twice weekly which is most commonly performed. Second, variability of definitions of PHT may lead to variation in prevalence estimates. In this regard, a study done in the USA[23] where PHT was defined as sPAP of ≥35 mm/Hg yielded a prevalence of PHT of 47%, which is close to the 42% prevalence in our study where PHT was defined as sPAP ≥35 mm/Hg. While when using sPAP of ≥45 mm/Hg to define PHT, the prevalence falls to 15.7%.[8] Third, variation in degrees of chronic volume overload can also affect the prevalence. Markers of chronic volume overload are not agreed on yet, hence, it is difficult to control this variation in studies.[24-26]

Our study found that the age and the duration of dialysis of patients had no relationship to PHT. This is similar to the result by Amin *et al*.[6] and Abasi *et al*.,[27] but different from the results by Yigla *et al*.[4] and Havlucu *et al*.[5] which found that PH was related to long-term HD therapy.

Our study found a relationship between EF and the presence PHT in patients on HD and patients not on HD. This is similar to the results found in other studies,[22,28-30] but different from the results of Havlucu *et al*.[5]

Our study found that Hb had no relationship to PHT (which means that anemia is an unlikely cause of overflow-associated PHT), while S. albumin was significantly lower in patients with PHT on HD. Amin *et al*.[6] also found similar result regarding Hb, however, he did not study S. albumin values, while Mousavi *et al*.[28] found that both Hb and S. albumin were significantly lower in patients with PHT on HD.

Our study found no relationship between dialysis access type and PHT which is similar to the results by Beigi *et al*., and Agarwal,[31,32] but different from result by Unal *et al*.[33] It is worth mentioning that Beigi *et al*. and Unal *et al*.[31,33] studied only patients with surgically created AV access, while our study included also catheter-based dialysis patients which means that overflow is less likely to be implicated in the pathogenesis of PHT regardless the dialysis access type, at least in our study population. Furthermore, Beigi *et al*. and Unal *et al*.[31,33] studied also the AVF flow and not just the AVF creation, and Beigi and his coworkers found a relationship between AVF flow and PHT, while Unal and his coworkers did not find such a relationship. One of the limitations of our study is that we did not include AVF flow. This difference in the results could be due to the difference in the duration of AVF creation.

Conclusions

1. PHT is more prevalent among patients on HD
2. EF is related to PHT
3. Duration of dialysis, age of patients, Hb, and dialysis access type had no relationship to PHT.

Recommendations

1. More studies are needed in our country regarding PHT in patients with variable stages of renal disease with larger sample sizes and different study designs with the inclusion of data and parameters that were missing in our study such as the duration of AVF creation
2. Periodic screening of patients with variable stages of renal disease (especially those on HD) for PHT.

Table 5: The relationship between, ejection fraction, hemoglobin and serum albumin levels and presence of pulmonary hypertension in the study groups

Parameters Group 1 (*n*=100)	PHT (*n*=42)	No PHT (*n*=58)	*P**
EF	53.0±1.02	54.1±2.0	0.001
Hb (g/dL)	9.7±1.57	9.1±1.49	0.06
Serum albumin (g/L)	35.1±1.98	33.5±3.11	0.004
Parameters Group 2 (*n*=96)	**PHT (*n*=12)**	**No PHT (*n*=84)**	***P****
EF	54.2±1.09	55.4±1.9	0.035
Hb (g/dL)	10.7±2.07	9.9±1.92	0.18
Serum albumin (g/L)	34.0±5.22	32.6±4.35	0.31

**t*-test was used. PHT: Pulmonary hypertension, EF: Ejection fraction, Hb: Hemoglobin

Table 6: The relationship between dialysis access and pulmonary hypertension in Group 1 (*n*=100)

Dialysis access	PHT, *n* (%)	No PHT, *n* (%)	*P**
AVF	36 (36)	50 (50)	0.94
CVC	6 (6)	8 (8)	

*Chi-square test was used, df=1. PHT: Pulmonary hypertension, CVC: Central venous catheter, AVF: Arteriovenous fistula

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Nil.

Conflicts of interest

There are no conflicts of interest.

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