Pulmonary hypertension in hemodialysis patients: frequency and risk factors

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Objective
The authors aimed to determine the prevalence of pulmonary hypertension in patients with end-stage kidney disease on regular hemodialysis (HD). The authors also aimed to study the possible correlation between the occurrence of pulmonary hypertension and fluid overload, arteriovenous fistula (AVF) blood flow, valvular calcification, and other laboratory variables.

Patients and methods
This cross-sectional descriptive study was conducted on 80 patients with end-stage kidney disease on regular HD for more than one year in Al Agoza Hospital in Cairo, Egypt. General data were collected. A transthoracic 2D echocardiography was done for all studied patients within one hour after HD. Pulmonary hypertension's definition was an estimation of pulmonary artery systolic pressure greater than 35 mmHg by echocardiography.

Results
Pulmonary hypertension (pulmonary artery systolic pressure >35 mmHg) presented in 21 (26.2%) patients, whereas mild (35–50 mmHg), moderate (51–70 mmHg), and severe pulmonary hypertension (>70 mmHg) presented in seven (8.8%), 10 (12.5%), and four (5%) patients, respectively. Pulmonary hypertension presented in 13 (62%) female patients vs eight (38%) male patients, which is of statistical significance (P<0.001). Mean duration of dialysis was significantly higher in patients with pulmonary hypertension (PHTN) than those without (8.54±3.53 years vs 3.88±1.01 years; P<0.001). Valvular calcification, fluid overload, and blood flow through AVF were significantly correlated to the development of PHTN.

Conclusion
Pulmonary hypertension in patients with end stage kidney disease (ESKD) on regular HD is frequent. Blood flow through AVF and chronic fluid overload may be involved in the development of PHTN in patients with ESKD who are on regular hemodialysis.

Keywords:
arteriovenous fistula, end-stage renal disease, hemodialysis, pulmonary hypertension, valvular calcification

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Introduction

Incoming evidence suggests that pulmonary hypertension, a recognized complication of end-stage kidney disease, is closely associated with cardiac, pulmonary, and systemic diseases and also with increased mortality [1]. Pulmonary hypertension has been reported as unrecognized threat in maintenance hemodialysis (HD) patients [2].

The prevalence of pulmonary hypertension may be 16%[3] up to 58% [4] in HD patients as reported by different studies. Regardless of the etiology, the morbidity and the mortality from long-standing pulmonary hypertension exceed that expected from the causative condition. Pulmonary hypertension involves vasoconstriction and obliteration of the lumen of small vessels in the lungs by plexiform lesions, resulting in increased resistance to flow [5].

Chronic volume overload, metabolic derangements affecting pulmonary vasculature, alterations in calcium and phosphate metabolism causing metastatic pulmonary artery calcification, and chronically increased blood flow from arteriovenous fistula (AVF) or arteriovenous graft, all these may predispose to elevated pulmonary pressures [6].

Most pulmonary hypertension (PHTN) cases in the population of patients with end-stage kidney disease receiving HD treatment through an arteriovenous access is secondary to heart diseases. However, unexplained pulmonary hypertension in this patient's population has been reported too [7], representing a distinct clinical syndrome in which pulmonary hypertension occurs shortly after the arteriovenous access formation,

sometimes even before starting HD treatment [8]. Cardiovascular disease is the most common cause of death in end-stage kidney disease [9]. Patients with end-stage kidney disease have a cardiovascular risk far greater than that explained by hypertension or other traditional cardiovascular lifestyle risk factors alone [10].

Patients and methods

This descriptive cross-sectional study was conducted on 80 patients with end-stage kidney disease on regular HD (aged from 18 to 60 years) for more than 1 year in Al Agoza Hospital in Cairo, Egypt, in the period between December 2017 and December 2018. The patients with a higher possibility of secondary pulmonary hypertension (those with a history of chronic obstructive or restrictive lung disease, heart failure, chronic thromboembolic disease, HIV infection, or bilharziasis) were excluded. All patients were subjected to full history and clinical examination. The general data of studied patients (age, sex, comorbidities, and drugs) and renal disease (cause of kidney failure, type of dialysis access, and duration of hemodialysis) were collected from the patients' medical files directly from them. Laboratory investigations were conducted, including intact parathormone hormone, which was measured by chemiluminescence immunoassay, with reference range of 10–93 pg/ml; serum calcium; serum phosphate; alkaline phosphatase; blood urea; serum creatinine; complete blood count; and serum albumin. A transthoracic 2D echocardiography was performed for the studied patients. Pulmonary artery systolic pressure (PASP) was measured by estimating transtricuspid valve regurge pressure gradient added to the estimated right atrial pressure. Echocardiography was done by a cardiologist within one hour after HD so as to avoid overestimation of PASP.

Ethical considerations

This study was approved by Ethical Committee, Faculty of Medicine, Assiut University (IRB; 17101044).

All patients were provided a detailed description of the procedures before being enrolled in this study, and a signed informed consent was obtained from them for participating in the study.

ClinicalTrials.gov Identifier: NCT03310229.

Statistical analysis

Data were collected and analyzed those using SPSS (Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in form of mean ± SD or median (range), whereas nominal data were expressed in the form of frequency (percentage). χ^2-test was used to compare the nominal data of different groups in the study, whereas Student's *t*-test was used in case of continuous data. *P* value was considered significant if less than 0.05. The level of confidence was kept at 95%; hence, a *P* value less than 0.05 indicated a significant association.

Results

The mean age of studied patients was 49.25 ± 9.41 years, with range between 20 and 60 years. Of the 80 studied patients, 42 (52.5%) were females. Duration of dialysis ranged from 1.5 to 13 years, with a mean duration of 4.73 ± 2.44 years. The most frequent cause of renal disease was diabetes mellitus (31.3%), followed by hypertension (25%), and obstructive uropathy (12.5%). Table 1 shows the demographic data of the studied patients.

Of the 80 studied patients, 21 (26.2%) had elevated PASP above 35 mmHg, whereas mild (35–50 mmHg), moderate (51–70 mmHg), and severe pulmonary hypertension (>70 mmHg) presented in seven (8.8%), 10 (12.5%), and four (5%) patients, respectively. Patients with pulmonary hypertension and those without had insignificant differences regarding age, but mean duration of HD was significantly higher in patients with pulmonary hypertension than those without (8.54 ± 3.53 vs 3.88 ± 1.01 years; $P < 0.001$). Pulmonary hypertension presented in 13 (62%) female patients vs eight (38%) male patients, which is of statistical significance ($P < 0.001$). Table 2 shows the characteristics of studied patients based on presence of pulmonary hypertension. Grades of PASP are shown in Fig. 1.

Data were expressed in form of mean (SD) and frequency (percentage). *P* value was significant if less than 0.05.

Correlations between PASP and other variables are shown in Table 3 and Figs. 2 and 3.

PASP had a significant positive moderate correlation with calcium level ($r = 0.413$, $P < 0.001$).

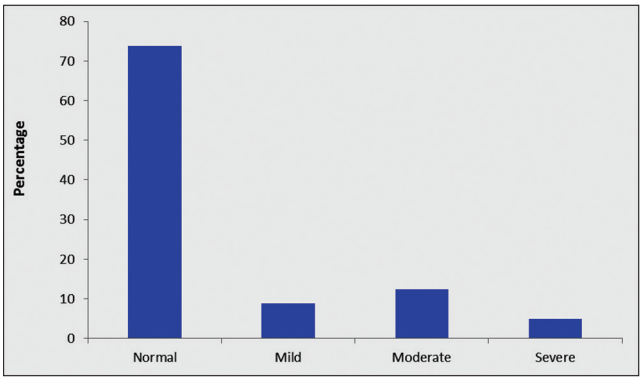
PASP had a significant positive weak correlation with hemoglobin level ($r=-0.297$, $P < 0.001$).

PASP had a significant positive weak correlation with phosphate level ($r = 0.367$, $P < 0.001$).

PASP had a significant positive moderate correlation with parathormone hormone ($r = 0.418$, $P < 0.001$).

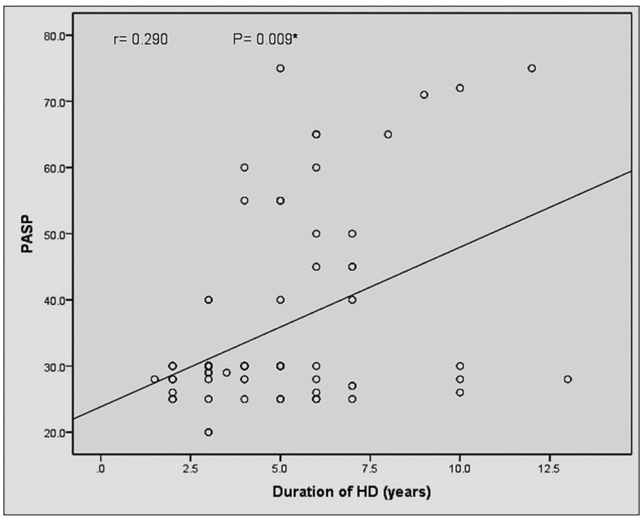
PASP had a significant positive moderate correlation with alkaline phosphatase ($r = 0.495$, $P < 0.001$).

Figure 1



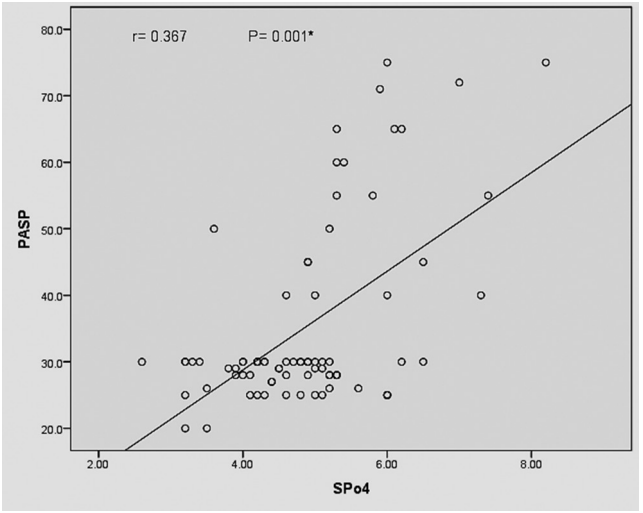
Grades of pulmonary artery systolic pressure in studied group.

Figure 2



Correlation of pulmonary artery systolic pressure with duration of dialysis.

Figure 3



Correlation of pulmonary artery systolic pressure with phosphate.

PASP had a significant positive weak correlation with duration of dialysis (r = 0.291, P < 0.001). Other correlations were insignificant.

Table 1 Demographic data of studied patients

	n=80
Age (years)	
Mean±SD (range)	49.25±9.41 (20.0-60.0)
Sex	
Male	38 (47.5)
Female	42 (52.5)
Duration of HD (years)	
Mean±SD (range)	4.73±2.44 (1.5-13.0)
Primary cause	
DM	25 (31.3)
HTN	20 (25)
Obstructive uropathy	10 (12.5)
NSAID abuse	8 (10.0)
ADPKD	6 (7.5)
Reflux nephropathy	5 (6.3)
Chronic UTI	1 (1.3)
FMF	1 (1.3)
Unknown cause	4 (5.0)

Data were expressed in form of mean±SD and frequency (percentage).ADPKD, adult polycystic kidney disease; DM, diabetes mellitus; FMF, familial Mediterranean fever; HD, hemodialysis; HTN, hypertension; NSAIDs, nonsteroidal anti-inflammatory drugs; UTI, urinary tract infection.

Table 2 Characteristics of studied patients based on presence of pulmonary hypertension

	Without PHTN [*n* (%)]	With PHTN [*n* (%)]	*P*
Age			
Mean±SD	48.99±8.76 (23-60.0)	51.5±10.11 (20-58)	0.345
Sex			
Male	30 (51)	8 (38)	<0.001
Female	29 (49)	13 (62)	
Duration of dialysis (years)			
Mean±(SD)	3.88±1.01 (1.5-6)	8.54±3.53 (5-13)	<0.001

PHTN, pulmonary hypertension.

A total of 69 (86.3%) patients had AVF, whereas Permicath presented in only 11 (13.8%) patients. The average interdialytic weight gain in the studied patients ranged between 1 and 6 kg. Of the studied patients, 15 (18.8%) patients had mitral and aortic valvular calcification. It was noticed that all patients who developed PHTN had AVF. A total of 15 (71.4%) patients with PHTN had valvular calcification, whereas none of those without PHTN had valvular calcification. The average interdialytic weight gain was significantly higher in patients with PHTN (P < 0.001). Table 4 shows possible risk factors in studied patients based on the presence of PHTN.

Discussion

There is a clear difference in the prevalence of pulmonary hypertension in HD patients in different studies. Our finding corresponded with the study by Tarrass and colleagues in 2006 in Casablanca [11], where the

Table 3 Correlation between pulmonary artery systolic pressure and other variables

Laboratory investigations	PASP	
	r	*P*
Calcium level (mg/dl)	0.413	<0.001
Hemoglobin (g%)	−0.297	<0.001
Platelets count (×10^9/l)	−0.001	0.991
Blood urea (mg/dl)	0.122	0.281
phosphate level (mg/dl)	0.367	<0.001
Serum albumin (mg/dl)	−0.217	0.053
Serum creatinine (mg/dl)	0.032	0.781
Parathormone hormone (pg/ml)	0.418	<0.001
Alkaline phosphatase (Ul/l)	0.495	<0.001
Duration of dialysis (years)	0.291	<0.001

Data were expressed in form of r value (indicated to strength of correlation), and *P* value (indicated to significance of correlation and considered significant if <0.05).PASP, pulmonary artery systolic pressure.

Table 4 Possible risk factors in studied patients based on presence of pulmonary hypertension

	Without PHTN	With PHTN	*P*
Vascular access			
AVF	48 (81.3)	21 (100)	0.03
Permicath	11 (18.7)	0	
Vulvular calcification	0	15 (71.4)	<0.001
Average interdialytic weight gain (kg)	2.26±0.79	4.62±0.76	<0.001

Data were expressed in form of mean±SD and frequency (percentage). *P* value was significant if <0.05. AVF, arteriovenous fistula; PHTN, pulmonary hypertension.

prevalence was 27%. Our finding is in contrast to that obtained by the study by Fabbian *et al.*[4] in 2011 in Italy, where the prevalence of pulmonary hypertension in their study was 58%, and also in contrary to the study by Faqih and colleagues, 2016, in Casablanca [3], where the prevalence was 16%.

The variability in the prevalence of pulmonary hypertension in different studies may be owing to the following: first, the timing of performance of echocardiography may affect the estimation of PASP plus the interdialytic weight gain. A higher prevalence of 58% in Italy may be owing to the estimation of PASP with echocardiogram a day after HD [4], whereas lower prevalence of 29% in a study by Amin *et al.*[12] may be owing to the estimation of PASP 4 h after the end of HD.

Second, varying definitions of PASP may have contributed to these varying percentages of prevalence. For example, in a study in USA, when the definition of pulmonary hypertension was an estimate of PASP greater than 45 mmHg by cardiac Doppler ultrasound, the prevalence was 19% [13]. However, in our study, the definition of pulmonary hypertension was an estimate of PASP greater than 35 mmHg by echocardiography [14].

In our study, 62% of patients with pulmonary hypertension were females, whereas males with pulmonary hypertension represented 38%. This agrees with the study by Mukhtar *et al.*[6] in 2014 in Pakistan where they found a high prevalence of pulmonary hypertension in female patients (52%). Moreover, Havlucu *et al.*[15] reported a high prevalence of pulmonary hypertension in female patients in their study in 2007 in turkey, where it was 60% compared with 40% in male patients.

This finding is in contrast to the results of the study by Dagli *et al.*[16] in 2009 where they did not find a significant correlation between sex and pulmonary hypertension. Our findings support many studies that have shown a high prevalence of pulmonary hypertension in female patients, and this may be explained by the frequency of pregnancy, where the pregnant women may have deep venous thrombosis causing subclinical pulmonary embolism, which may contribute to the development of pulmonary hypertension in HD female patients.

It was noticed in our study that there were insignificant differences regarding age between patients with pulmonary hypertension and those without. This disagrees with Lee's finding in a study in 2016 in Korea [17], where he found a significant correlation between the older age and the development of pulmonary hypertension. Our finding agrees with Mukhtar *et al.*[6] who reported no relation between age and pulmonary hypertension.

Our study showed that the duration of HD was significantly higher in patients with pulmonary hypertension than those without (8.54 ± 3.53 vs 3.88 ± 1.01 years). This agrees with the results reported by Mukhtar *et al.* in 2014 in Pakistan [6], Fabbian *et al.* in 2011 in Italy [4], and Agarwal in 2012 in USA [18]. All found a significant association between the development of pulmonary hypertension and the dialysis duration.

On the contrary, Mousavi *et al.*[19] found no relation between the duration of HD and pulmonary hypertension. Very few studies like the one by Mousavi *et al.*[19] reported any correlation between dialysis duration and pulmonary hypertension, whereas so many studies yielded a significant correlation. This may be explained by the longer period of exposure of the vascular endothelium to hyperphosphatemia (which is very common in those patients as noticed in our study) and chronic inflammation with HD, which may contribute to the hardening and stiffening of vascular lining.

We used echocardiography to estimate PASP as well as to detect the presence of any valvular calcifications. A total of 15 patients had mitral and aortic valvular calcifications represented 71.4% of patients with pulmonary hypertension (n = 21). This significant correlation between valvular calcifications and pulmonary hypertension in our study agrees with the study by Li and colleagues conducted in 2014 in China [2]. On the contrary, Amin *et al*.[12] found no relation between valvular and even vascular calcifications and pulmonary hypertension.

Our study demonstrated a significant association between calcium, phosphorus, and alkaline phosphatase and pulmonary hypertension, which is in contrary to the study by Fabbian *et al*.[4] in Italy who reported no relation between calcium, phosphorus, and alkaline phosphatase and pulmonary hypertension.

Our study showed a significant correlation between high levels of parathormone hormone and the development of pulmonary hypertension, which agrees with Akmal *et al*.[20] in USA; they stated that high levels of parathormone hormone provoked pulmonary artery calcifications and pulmonary hypertension. Other studies reported no relation between parathormone hormone and pulmonary hypertension, such as Havlucu *et al*.[15] in turkey and Abdelwahab *et al*.[21] in Egypt.

In addition, our study demonstrated that anemia is significantly correlated to pulmonary hypertension. This may be explained by the hypoxia and the hyperdynamic circulation induced by anemia, which lead to increase in the blood flow, and cardiac output (especially almost all of those patients have a degree of fluid overload). Increased cardiac output may contribute with other factors to the development of pulmonary hypertension. This agrees with the finding of Navaneethan *et al*.[22] in USA.

The average interdialytic weight gain was significantly higher in patients with pulmonary hypertension than those without (4.62 ± 0.76 vs 2.2 ± 0.79 kg). This significant correlation has been found by other studies like the study by Fabbian *et al*.[4] in Italy. The average interdialytic weight gain in the study by Fabbian and colleagues was 2.1 ± 0.1 kg in patients with pulmonary hypertension vs 1.3 ± 0.9 kg in those without pulmonary hypertension.

Our study demonstrated a significant correlation between the presence of AVF and pulmonary hypertension. Of the 48 patients having AVF, 21 had pulmonary hypertension. It was noticed that all patients having permanent catheter did not have pulmonary hypertension. This may be explained by the increase in blood flow and cardiac output, which may contribute to the development of pulmonary hypertension.

This finding agrees with Nakhoul *et al*. [23], where they reported a significant correlation AVF and pulmonary hypertension. They also have shown in their study a significant decline in PASP and cardiac output in HD patients who underwent successful kidney transplantation or temporary closure of AVF.

Conclusion

Pulmonary hypertension in patients with ESKD who are on regular HD is frequent and deserves much more attention. Blood flow through AVF, chronic fluid overload, vascular calcification, and longer periods of HD may be implicated in the pathogenesis of pulmonary hypertension in patients with ESKD who are on regular HD.

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Conflicts of interest

There are no conflicts of interest.

References

1 Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, *et al*. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62 (25 Suppl):D34–D41.

2 Li Z, Liu S, Liang X, Wang W, Fei H, Hu P, *et al.* Pulmonary hypertension as an independent predictor of cardiovascular mortality and events in hemodialysis patients. Int Urol Nephrol 2014; 46:141–149.

3 Faqih SA, Noto-Kadou-Kaza B, Abouamrane LM, Mtiou N, El Khayat S, Zamd M, *et al.* Pulmonary hypertension: prevalence and risk factors. IJC Heart Vasc 2016; 11:87–89.

4 Fabbian F, Cantelli S, Molino C, Pala M, Longhini C, Portaluppi F. Pulmonary hypertension in dialysis patients: a cross-sectional Italian study. Int J Nephrol 2011; 2011:283475.

5 Rubin LJ. Pathology and pathophysiology of primary pulmonary hypertension. Am J Cardiol 1995; 75:51A–54AA.

6 Mukhtar KN, Mohkumuddin S, Mahmood SN. Frequency of pulmonary hypertension in hemodialysis patients. Pak J Med Sci 2014; 30:1319.

7 Abassi Z, Nakhoul F, Khankin E, Reisner SA, Yigla M. Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. Curr Opinion Nephrol Hypertens 2006; 15:353–360.

8 Yigla M, Banderski R, Azzam ZS, Reisner SA, Nakhoul F. Arterio-venous access in end-stage renal disease patients and pulmonary hypertension. Therap Adv Respir Dis 2008; 2:49–53.

9 Husain-Syed F, McCullough PA, Birk H-W, Renker M, Brocca A,

Seeger W, *et al*. Cardio-pulmonary-renal interactions: a multidisciplinary approach. J Am Coll Cardiol 2015; 65:2433–2448.

10 Ting SM, Hamborg T, McGregor G, Oxborough D, Lim K, Koganti S, *et al*. Reduced cardiovascular reserve in chronic kidney failure: a matched cohort study. Ame J Kidney Dis 2015; 66:274–284.

11 Tarrass F, Benjelloun M, Medkouri G, Hachim K, Benghanem MG, Ramdani B. Doppler echocardiograph evaluation of pulmonary hypertension in patients undergoing hemodialysis. Hemodial Int 2006; 10:356–359.

12 Amin M, Fawzy A, Hamid MA, Elhendy A. Pulmonary hypertension in patients with chronic renal failure: role of parathyroid hormone and pulmonary artery calcifications. Chest 2003; 124:2093–2097.

13 Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, *et al*. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997; 134:44–54.

14 Kalantar-ZadehKamyar M, Regidor Deborah L, Kovesdy Csaba P, David VW, Suphamai B, Horwich Tamara B, Fonarow Gregg C. Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis. Circulation 2009; 119:671–679.

15 Havlucu Y, Kursat S, Ekmekci C, Celik P, Serter S, Bayturan O, *et al*. Pulmonary hypertension in patients with chronic renal failure. Respiration 2007; 74:503–510.

16 Dagli CE, Sayarlioglu H, Dogan E, Acar G, Demirpolat G, Ozer A, *et al*. Prevalence of and factors affecting pulmonary hypertension in hemodialysis patients. Respiration 2009; 78:411–415.

17 Lee SB. Pulmonary hypertension in chronic kidney disease: what could change the fate? Kidney Res Clin Pract 2016; 35:63.

18 Agarwal R. Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. Nephrol Dial Transplant 2012; 27:3908–3914.

19 Mousavi S, Mahdavi MM, yahyazadeh H, Azadi M, Rahimzadeh N, Yousef NH, *et al.* Pulmonary hypertension and predisposing factors in patients receiving hemodialysis. Iran J Kidney Dis 2008; 2:29–33.

20 Akmal M, Barndt RR, Ansari AN, Mohler JG, Massry SG. Excess PTH in CRF induces pulmonary calcification, pulmonary hypertension and right ventricular hypertrophy. Kidney Int 1995; 47:158–163.

21 Abdelwhab S, Elshinnawy S. Pulmonary hypertension in chronic renal failure patients. Am J Nephrol 2008; 28:990–997.

22 Navaneethan SD, Roy J, Tao K, Brecklin CS, Chen J, Deo R, *et al*. Prevalence, predictors, and outcomes of pulmonary hypertension in CKD. J Am Soc Nephrol 2016; 27:877–886.

23 Nakhoul F, Yigla M, Gilman R, Reisner SA, Abassi Z. The pathogenesis of pulmonary hypertension in haemodialysis patients via arterio-venous access. Nephrol Dialy Transplant 2005; 20:1686–1692.