Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients

Mordechai Yigla[1], Oren Fruchter[1], Doron Aharonson[2], Noa Yanay[3], Shimon A. Reisner[2], Moshe Lewin[3] and Farid Nakhoul[4]

[1]Division of Pulmonary Medicine, Rambam Health Care Campus and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology Haifa, Haifa, Israel; [2]Department of Cardiology, Rambam Health Care Campus and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology Haifa, Haifa, Israel; [3]Department of Nephrology, Rambam Health Care Campus and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology Haifa, Haifa, Israel and [4]Ambulatory Nephrology Unit, Rambam Health Care Campus and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology Haifa, Haifa, Israel

Pulmonary hypertension in patients with end-stage renal disease on hemodialysis is a newly described entity. To determine its impact, we measured selected clinical variables in the survival of 127 hemodialysis patients. Overall, pulmonary hypertension was found in 37 of these patients; it was already prevalent in 17 of them before initiation of dialysis and was associated with severe cardiac dysfunction. In the other 20 it developed after dialysis began, without obvious cause. These two subgroups of patients had similar survival curves, which were significantly worse in comparison to those without pulmonary hypertension. Following the initiation of hemodialysis, 20 patients with otherwise matched clinical variables survived significantly longer than the 20 who developed pulmonary hypertension after dialysis began. With univariate analysis, significant hazard ratios were found for age at onset of hemodialysis therapy (1.7), valvular diseases (1.8), pulmonary hypertension prevalence before hemodialysis (3.6) and incident after hemodialysis (2.4) for predicting mortality. In a multivariable Cox proportional hazard model, the development of pulmonary hypertension both before and after initiation of hemodialysis had significantly increased odds ratios and remained an independent predictor of mortality. Our study shows the incidence of pulmonary hypertension, after initiation of hemodialysis therapy, is a strong independent predictor of mortality nearly equal to that associated with long-standing severe cardiac abnormalities.

Kidney International (2009) **75,** 969–975; doi:10.1038/ki.2009.10; published online 11 February 2009

KEYWORDS: end-stage renal disease; hemodialysis; pulmonary hypertension; survival

Correspondence: *Mordechai Yigla, Division of Pulmonary Medicine, Rambam Health Care Campus, POB 9602, Haifa 31096, Israel. E-mail: m_yigla@rambam.health.gov.il*

Received 31 October 2007; revised 17 December 2008; accepted 23 December 2008; published online 11 February 2009

Pulmonary hypertension (PHT) is an uncommon disease characterized by increased pulmonary artery pressure (PAP) and resistance. The disease results from many diverse mechanism among which the most common are cardiac, pulmonary, and systemic diseases. PHT is associated with increased morbidity and mortality. For example, the median survival for untreated primary PHT patients is 30 months.

The vast majority of PHT in the population of end-stage renal disease (ESRD) patients receiving hemodialysis (HD) therapy through a surgical arterio-venous (A-V) access is secondary to heart conditions. However, unexplained PHT in this patient's population has been described too,[1–5] representing a distinct clinical syndrome in which PHT occurs shortly after the A-V access formation, sometimes even before starting HD therapy,[6] mainly among patients with significantly (A-V access mediated) increased cardiac output (CO), and may regress after reduction of CO by temporary A-V access closure or after reversing the uremia by successful kidney transplantation.[1] The pathogenesis of this syndrome is considered to be ESRD-related endothelial dysfunction that restricts the ability of the pulmonary vessels to accommodate the A-V access-mediated elevated CO.[3–5] In a preliminary observation including 58 HD patients,[1] we recorded higher mortality rates among HD patients with unexplained PHT. This study was designed to extend existing data regarding the correlation between PHT and mortality among ESRD patients receiving chronic HD therapy.

RESULTS

The characteristics of the entire study population and of subgroups of patients with and without PHT are presented in Table 1. There were 78 males and 49 females with a male:female ratio of 1.59. The mean ± s.d. and median age at the onset of HD therapy were 61.6 ± 14 and 63 years, respectively. Seventy-seven percent of the patients were in the sixth to eighth decades of life at the onset of HD therapy. The most common etiology of the end-stage renal failure was diabetes mellitus, which was found in 41 (32.3%) patients. Ischemic heart disease was the most common comorbidity,

Table 1 | Patient characteristics

	All	No PHT	PHT prevalent on entering HD	PHT incident after initiation of HD
No. of patients	127	90 (70.9%)	17 (13.4%)	20 (15.7%)
Gender				
Male	78 (53.5%)	56 (62.2%)	10 (58.8%)	12 (60%
Female	49 (46.5%)	34 (37.8%)	7 (41.2%)	8 (40%)
M/F ratio	1.59	1.67	1.33	1.5
Age at onset of HD (years)				
Mean ± s.d.	61.6 ± 14	61.2 ± 13.4	63.3 ± 14	62.9 ± 17.4
Range	22–89	22–81	29–79	28–89
Median	63	63	65	65
Etiology of kidney disease				
Diabetes mellitus	41 (32.3%)	32 (35.6%)	4 (23.55)	5 (25%)
Chronic pyelonephritis	15 (11.8%)	8 (8.9%)	3 (17.6%)	4 (20%)
Hypertension	13 (10.2%)	9 (10%)	3 (17.6%)	1 (5%)
Nephrolithiasis	12 (9.4%)	7 (7.7%)	2 (11.8%)	3 (15%)
Polycystic kidney	11 (8.7%)	7 (7.7%)	2 (11.8%)	2 (10%)
Glomerulonephritis	8 (6.3%)	6 (6.7%)	1 (5.9%)	1 (5%)
Unknown	27 (21.3%)	21 (23.3%)	4 (23.5%)	4 (20%)
Co-morbid condition				
Ischemic heart disease	58 (45.7%)	35 (38.9%)	11 (64.7%)	12 (60%)
Diabetes mellitus	41 (32.3%)	27 (30%)	7 (41.2%)	7 (35%)
Hypertension	13 (10.2%)	5 (5.5%)	6 (35.3%)	2 (10%)
COPD	4 (3.1%)	2 (2.2%)	1 (5.9%)	1 (5%)
Medications				
Beta blockers	69 (54.3%)	47 (52.2)	11 (64.7%)	11 (55%)
Calcium channel blockers	35 (27.5%)	22 (24.4%)	5 (29.4%)	8 (40%)
ACE inhibitors	91 (71.6%)	62 (68.9%)	15 (88.2%)	14 (70%)
*Duration of HD (years)**				
Mean ± s.d.	4.7 ± 2.4	5.9 ± 2.7	4.1 ± 2.9	4.4 ± 3.4
Range	2–12	2–12	2–10	2–10
A-V access location				
Brachial	37 (29.1%)	27 (30%)	7 (41.2%)	3 (15%)
Radial	90 (70.9%)	63 (70%)	10 (58.8%)	17 (85%)
Mortality*	77 (60.6%)	47 (52.2%)	14 (82.35%)	16 (80%)

ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; HD, hemodialysis; PHT, pulmonary hypertension.
*$P<0.05$.

presenting in 58 (45.7%) patients. Ninety patients underwent HD therapy through radial and 37 through brachial vascular access. The mean duration of HD therapy and follow-up was 4.7 ± 2.4 years, range 2–12 years.

Pulmonary hypertension of $\geqslant$45 mm Hg was found in 37 (29.1%) patients. In 17 (13.4%) of them it was present before entering the HD program, whereas in the entire 20 patients (15.7%) it was incident after initiation of HD therapy. These two subgroups had similar mean systolic PAP values (52 ± 6 vs 54 ± 5 mm Hg, respectively, $P = 0.37$).

For patients with PHT incident after the initiation of HD therapy, the time interval from initiation of HD to the first echo study that showed PHT was <1 year in 15 patients (75%) and 1–5 years in five patients (25%). Extensive work-up failed to disclose a cause for the PHT in this subgroup of patients.

Data about the cardiac status are shown in Table 2. Fifty-eight patients (45.7%) had ischemic heart disease and 65 patients (51.2%) had at least one-left ventricular abnormality —dilatation (53), hypertrophy (60), systolic dysfunction (26), and diastolic dysfunction (38). Thirty-five patients (27.6%) had left ventricular segmental wall abnormalities reflecting old myocardial infarction. Thirty-three patients (25.6%) had significant valvular abnormalities (moderate to severe mitral regurgitation—26, and moderate to severe aortic regurgitation—6, severe aortic stenosis—1).

The three subgroups of patients had similar clinical characteristics with respect to gender and age distribution, etiology of kidney failure, type and frequency of co-morbid conditions, list of medication used, and A-V access location, and the differences between the parameters among the three subgroups were not statistically significant (Table 1). As shown in Table 2, patients without PHT and with PHT incident after initiation of HD therapy had similar cardiac status as reflected by the frequency of ischemic heart disease and by the distribution of echocardiographic abnormalities,

Table 2 | Cardiac status

	'A' No PHT (n=90)	'B' PHT prevalent before HD (n=17)	'C' PHT incident after HD (n=20)	'A' vs 'B'	'A' vs 'C'	'B' vs 'C'
Ischemic heart disease	35	11	12	NS	NS	NS
Echocardiographic abnormalities						
Valvular						
Mitral reg. mod-severe	9 (10%)	15 (88.2%)	2 (10%)	<0.0001	NS	P=0.008
Aortal reg. mod-severe	3 (3.3%)	2 (11.8%)	1 (5%)	NS	NS	NS
Mitral stenosis mod-severe	0	0	0	NS	NS	NS
Aortic stenosis mod-severe	0	1	0	NS	NS	NS
Left ventricular						
Dilatation[a]	32 (35.6%)	16 (94.1%)	5 (25%)	0.06	NS	NS
Hypertrophy[b]	43 (47.8%)	11 (64.7%)	6 (30%)	NS	NS	NS
Systolic dysfunction[c]	11 (12.2%)	15 (88.2%)	0	<0.0001	NS	0.004
Diastolic dysfunction	26 (28.9%)	7 (41.2%)	5 (25%)	NS	NS	NS
Segmental abnormalities	20 (22.2%)	13 (76.5%)	2 (10%)	0.02	NS	0.058

HD, hemodialysis; NS, not significant (P>0.05); PHT, pulmonary hypertension.
[a]Cavity volume >90ml/m^2.
[b]Mass index >100g/m^2 (females) >130g/m^2 (males).
[c]Fractional shortening <25%.

Table 3 | Comparison of data between survivors and non-survivors

Variable	Died (n=77)	Lived (n=50)	P-value
Gender			
Male	39	29	
Female	38	21	0.5
Age at onset of HD			
(Mean ± s.d., years)	66.6 ± 10.8	52.5 ± 15.3	<0.0001
No. of patients >63 years	48	15	0.0005
Dialysis access			
Radial	19	18	0.23
Brachial	58	32	
PHT >45 mm Hg			
Prevalent before HD	14	3	0.03
Incident after HD	16	4	0.03
Diabetes mellitus	27	14	0.7
Cardiac status			
Ischemic heart diseases	41	17	0.248
Left ventricular dysfunction	18	8	0.547

HD, hemodialysis; PHT, pulmonary hypertension.

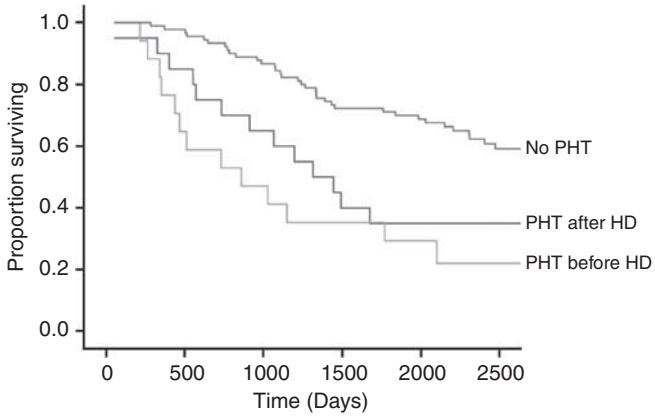

Figure 1 | Survival curves. The survival curves of the subgroups of patients without and with pulmonary hypertension (PHT) prevalent before or incident after onset of hemodialysis. Subgroups of patients with PHT had similar survival curves, which were significantly lower when compared with patients without PHT. HD, hemodialysis; PHT, pulmonary hypertension.

and both had better cardiac status as compared with the subgroup of patients with PHT prevalent before initiation of HD (significantly lower frequency of significant valvular abnormalities, left ventricular systolic dysfunction, and segmental wall abnormalities).

Survival data

Survival data for all the patients and for subgroups of patients without PHT and with PHT are presented in Tables 1 and 3 and in Figure 1. Subgroups of patients with PHT on starting of HD therapy and with PHT incident after initiation of HD therapy had a similar duration of HD therapy (or follow-up), which was significantly shorter than that of their counterparts without PHT (4.1 ± 2.9 and 4.4 ± 3.4 vs 5.9 ± 2.7, respectively). The significantly shorter duration of HD therapy among patients with PHT is attributed to the survival disadvantage of this disease. Overall, 77 (60.6%) patients died during the follow-up period. The 1-, 3-, and 5-year survival rates were 90.6, 66.9, and 52.8%, respectively. As a group, HD patients with PHT had significantly lower survival rates compared with their counterparts without PHT, as manifested by 1-, 3-, and 5-year survival rates of 78.6

vs 96.5, 42.9 vs 78.8, and 25.2 vs 66.4%, respectively (log-rank $P=0.0001$). Subgroups of patients with PHT incident after initiation of HD therapy and with PHT present before initiation of HD therapy had similar survival curves, and both had lower survival rates as compared with patients without PHT (log-rank $P=0.006$ for the comparison of patients without PHT and patients with PHT occurring after the initiation of HD and <0.0001 for the comparison of patients without PHT and patients with PHT present before the initiation of HD; Figure 1).

Non-survivors were significantly older on initiating HD (66.6 ± 10.8 vs 52.5 ± 15.3, $P<0.0001$), and had a significantly higher prevalence of PHT (30 vs 7, $P=0.035$), either incident after (16 vs 4, $P=0.03$) or prevalent at (14 vs 3, $P=0.03$) initiation of HD therapy.

The survival of 20 HD patients without PHT who matched the group of patients with PHT incident after initiation of HD therapy in their age, gender, etiology of kidney disease, location of A-V access, and co-morbidities was significantly longer, $P=0.0012$ in the log-rank test.

The results of the univariable analysis for predictors of mortality for the whole study population are shown in Table 4. The age at onset of HD therapy, and presence of significant valvular disease and PHT either prevalent before or incident after initiation of HD therapy were associated with an increased risk of death. Gender, DM, any parameter of left ventricular dysfunction alone or in combination, and location of A-V access were not associated with increased mortality rates.

In a multivariable Cox proportional hazard model, PHT remained the only independent predictor of all-cause mortality (Table 4). Compared with patients without PHT, the adjusted hazard ratios for mortality were 3.6 for PHT present before initiation of HD (95% CI 1.8–7.0, $P=0.0002$) and 2.1 for PHT that developed after the initiation of HD (95% CI 1.1–4.1, $P=0.02$). Using pulmonary pressure as a continuous variable in the whole study population, the adjusted hazard ratio (HR) for mortality was 1.5 for each 10 mm Hg increase in PAP (95% CI 1.2–1.9, $P=0.0007$).

DISCUSSION

Earlier studies have shown that the most common predictors of adverse outcome among the population of HD patients were age at onset of HD therapy and the extent of co-morbidities.[7] Analysis of this single-center cohort of 127 ESRD patients (33% with PHT) undergoing HD therapy through A-V access confirmed these findings. Age at initiation of HD therapy (HR: 1.7) and presence of significant valvular dysfunction, and moderate to severe regurgitation of the mitral and/or the aortic valve (HR 1.8) were the leading conditions with increased risk for death among this study population.

Diabetes mellitus, a well-recognized threat and a poor prognostic factor among HD patients, was not associated with an increased risk of death in this cohort, probably because of the small sample size. The more speculative option that HD patients with diabetes mellitus complications do not tend to develop PHT has yet to be proven.

This study has confirmed our earlier observation that in the population of HD patients, presence of PHT is associated with a significantly greater risk of death. The 1-, 3-, and 5-year survival rates of patients with and without PHT were 78.6 vs 96.5, 42.9 vs 78.8, and 25.2 vs 66.4%, respectively. Similar to other conditions, such as collagen vascular diseases, in which PHT is associated with a survival disadvantage, mortality rates of HD patients with PHT exceed those of their counterparts without PHT.[8,9] Of note, subgroups of patients with PHT prevalent before and incident after initiation of HD therapy had similar survival curves, which were significantly shorter compared with their counterparts without PHT.

Cardiac dysfunction, a common co-morbid condition in ESRD patients and the most common cause of PHT, was frequent in the study population. Detailed analysis has shown that the subgroups of patients with PHT incident after initiation of HD and without PHT at any time had similar cardiac status. Both subgroups had significantly better cardiac status as manifested by significantly lower frequency of valvular abnormalities and left ventricular dysfunctions as compared with the sub-group of patients with PHT prevalent on entering HD therapy. In a uni-variant and a multi-variant analysis of the whole study population, only the valvular abnormalities had reached the level of statistical significance.

This study stratifies two phenotypes of pre-dialysis patients, without and with PHT. In the former, some patients (subgroup 'C') develop unexplained PHT after receiving A-V access and initiating HD therapy. In an attempt to disclose masked cardiac dysfunction as a cause for this entity, we

Table 4 | Univariable and multivariable Cox regression models for death

	Univariable		Multivariable	
	Hazard ratio (95% CI)	P (χ^2)	Hazard ratio (95% CI)	P (χ^2)
Age at onset of HD (per 10 years increase)	1.7 (1.3–2.1)	<0.0001	1.6 (1.3–2.0)	<0.0001
Valvular disease	1.8 (1.0–3.1)	0.049	0.9 (0.5–1.7)	0.91
PHT				
No PHT	1.0 (Referent)	—	1.0 (Referent)	—
Present before HD	3.6 (1.9–4.8)	<0.0001	3.6 (1.8–7.0)	0.0002
Incident after HD	2.4 (1.2–4.5)	0.009	2.1 (1.1–4.3)	0.02

CI, confidence interval; HD, hemodialysis; PHT, pulmonary hypertension.

compared the cardiac status of the patients with PHT incident after initiation of HD with that of their counterparts without PHT at any time and found no difference. Thus we may assume that this entity cannot be attributed to existing cardiac abnormality.

In a multi-variant analysis, the HRs for death of ESRD patients with PHT incident after initiation of HD therapy and with PHT prevalent on initiation of HD therapy were 3.6 and 2.1, respectively. In other words, the risk of death for ESRD patients in whom PHT incident after A-V access formation and initiation of HD therapy was close to that of their counterparts who entered the HD program with PHT that is associated with long-standing severe cardiac dysfunction.

The entity of PHT in ESRD incidents after initiation of HD therapy is relatively new. In an earlier study, we reported a shorter life expectancy among HD patients with PHT.[1] However, we had some concerns regarding the findings, mostly because of the small sample size. This study extends our former observation that the development of PHT after A-V access formation and initiation of HD therapy is associated with a survival disadvantage.

The demonstration that PHT incident after onset of HD therapy is a strong independent risk factor for death has significant clinical implication. On one hand, HD therapy prolongs the lives of ESRD patients. On the other hand, some ESRD patients do not tolerate the hemodynamic changes in the area of the HD therapy through a surgically created A-V access and develop PHT with exceedingly high mortality rates.

The relatively small number of patients and the retrospective nature of this study carry a risk for bias. Statistical analysis for the entire study population and a sub-population analysis as well as matched analysis showed consistently that PHT either prevalent before or incident after initiation of HD therapy is a strong independent predictor for death.

In attempting to validate the findings of this study, we compared the epidemiological features of the study population with the data recorded on 10,000 HD patients from the Israel Center for HD Therapy and Kidney Transplantation Registry. The patient gender, age distribution, etiology of ESRD, and distribution of co-morbid conditions were similar. For example, the male:female ratio of 1.59 vs 1.56, mean and median ages at initiation of HD therapy of 61.6 and 63 years vs 63.5 and 67.3 years assured that the sample of patients included in the study is representative of the population of HD patients. However, it should be noted that the 1-, 3-, and 5-year mortality rates of the study population were significantly lower than those recorded in the national registry (9.4 vs 19, 33.1 vs 42.6, and 47.2 vs 65%), probably reflecting a single center's experience with a limited number of patients. Alternately, it might express better supportive medical care and improving dialysis techniques.

Many studies have looked at the predictors of mortality among ESRD patients on HD therapy.[10–12] Most incorporate into the survival analysis, in addition to epidemiological and clinical parameters, biochemical variables that reflect the quality of the HD therapy as well as the supportive care. As our study pertains to the impact of PHT on the outcome of ESRD patients on HD therapy at a single HD center providing therapy during a single decade, we felt that adding biochemical parameters to the survival analysis would not add to the understanding of this phenomenon.

PHT in HD patients has some unique characteristics that differ from other forms of the disease.[13,14] PAP values tend to regress after temporary closure of the A-V access (reduction of CO) or after successful kidney transplantation (amelioration of uremia). In earlier studies, we showed that the pathogenesis of this syndrome is uremic-induced endothelial dysfunction that reduces the ability of the pulmonary vasculature to accommodate the A-V access-mediated elevated CO results in the development of PHT.

Clinical significance

The presence of PHT in ESRD patients presents a therapeutic dilemma, as it is associated with significantly increased mortality rates. Patients entering the HD program should be screened for PHT before entering the program and on an annual basis thereafter. For patients with pre-existing PHT, kidney transplantation should be considered. The dilemma of PHT that is incident after initiation of HD therapy is more complicated. This form of PHT is generated by the life-saving HD therapy on the one hand and is associated with survival disadvantage on the other hand. In this set-up, screening of ESRD patients scheduled for initiation of long-term HD for sub-clinical PHT is recommended. The reversibility of this form of PHT following kidney transplantation is encouraging, and patients with significant PHT incident after initiation of HD therapy should be encouraged to seek a transplant. Surgical reduction of oversized A-V access should be considered in patients with PHT and extremely high CO who show a reduction of both CO and PHT values following temporary closure of their A-V access in the echocardiography laboratory. Peritoneal dialysis, another therapeutic alternative in some patients, is not attractive as recent studies have shown that the survival curves of patients with this mode of renal replacement therapy is similar to the survival curves of HD patients.[12]

MATERIALS AND METHODS

Study population

Patients' selection. A list of all patients undergoing chronic HD therapy in the Dialysis Unit at Rambam Health Care Campus, a 900-bed primary and tertiary, university-affiliated hospital, from 1995 to 2005 was retrieved from the computerized hospital database. Patients were included in the study if they had at least two Doppler echocardiography studies, one of them carried out before and another one after initiation of HD therapy. Patients with only one echo study were also eligible, if the echo study was carried out after initiation of HD therapy and had shown normal PAP values,

assuming that the pre-HD PAP values were normal. The study was approved by the local institutional review board.

Patient evaluation. Demographic data (age, gender, co-morbid conditions, and medications used) and data regarding kidney disease status: etiology of renal failure, A-V access formation date, access location (brachial, radial), and date of onset of HD therapy, were recorded. Co-morbid conditions were documented by a consultant nephrologist from the HD unit (FN) who was familiar with the patient's case history from the dialysis unit records, hospital discharge summaries, medication lists, consultation notes, and results of imaging tests. To be considered, the co-morbid condition had to be active, or currently controlled with ongoing treatment.

The following domains of active co-morbid disease were considered:

(1) Ischemic heart disease—As evidenced by earlier myocardial infarction, angina pectoris, positive coronary angiography, positive exercise or thallium or dobutamine stress test, echocardiographic evidence of left ventricular wall segmental abnormalities.
(2) Left ventricular dysfunction—a history of pulmonary edema and/or moderate to severe left ventricular dysfunction defined as echocardiographic or left ventricular fractional shortening $<25\%$.
(3) Peripheral vascular disease including aorta, renal, lower limb, and cerebral–vascular disease either symptomatic (CVA, claudicating, amputation) or of significant stenosis ($>70\%$) on vascular imaging or Doppler ultrasound.
(4) Diabetes mellitus type I or type II.
(5) Collagen vascular disease, such as systemic vasculitis, scleroderma, systemic lupus erythematosis, and rheumatoid arthritis, either active or requiring treatment.
(6) Other significant pathology severe enough to affect survival in the general population, such as chronic obstructive pulmonary disease, psychotic illness, cirrhosis, peptic ulcer, etc.

Echocardiography. The patients underwent a standard 2D, M-mode, Doppler echocardiography study within 2 h from the end of HD therapy while they were as close as possible to their dry weight. The form presented to the echocardiographist noted that the patient was receiving HD therapy, but it was not noted whether he/she had A-V access elsewhere. A tricuspid regurgitation systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler echocardiography probe. Systolic right ventricular (or pulmonary artery) pressure was calculated using the modified Bernoulli equation: PAP $= 4 \times$ (tricuspid systolic jet)$^2 + 10$ mm Hg (estimated right atrial pressure).[15] The accuracy of systolic PAP estimation by Doppler echocardiography in our laboratory has been published earlier.[16] PHT was defined as a systolic PAP of more than 45 mm Hg. The patients were categorized into three subgroups according to timing of PHT onset:

Sub-group 'A'—No PHT at any time.
Sub-group 'B'—PHT present before starting HD therapy.
Sub-group 'C'—PHT incident after initiation of HD therapy.

Records of patients with PHT incident after initiation of HD therapy were evaluated by a consultant pulmonologist (MY) to uncover potential causes of PHT. This included history, physical examination, chest radiograph and CT, pulmonary function tests, arterial blood gases and oxygen saturation, and ventilation–perfusion lung scan.

The echocardiographic findings were categorized according to the following list[17]:

(1) Significant valvular abnormality—moderate to severe stenosis and/or regurgitation of mitral and/or of the aortic valve.
(2) Left ventricular abnormality:
   a. Left ventricular dilatation—cardiac cavity >90 ml/m^2.
   b. Left ventricular hypertrophy—(mass index >100 g/m^2 (females), >131 g/m^2 (males)).
   c. Left ventricular systolic dysfunction—fractional shortening $\leqslant 25\%$.
   d. Left ventricular diastolic dysfunction.
(3) Left ventricular wall segmental abnormalities.

To investigate the etiology of PHT incident after initiation of HD therapy, the frequencies of the above-mentioned cardiac abnormalities were compared between this subgroup of patients and the sub-groups of patients without PHT and with PHT prevalent before starting HD.

Follow-up. The follow-up period was calculated from the onset of HD therapy to death. For survivors, 31 December 2007 was the last day of follow-up.

Data analysis. The differences between survivors and non-survivors were assessed using *t*-test for continuous variables and the chi-square test for categorical variables. Mortality data were expressed by the Kaplan–Meier survival curves and were compared using the log-rank test. The effect of prognostic factors on mortality was assessed within the whole population and for the three subgroups of patients: without PHT (reference group), with PHT present on initiation of HD and with PHT incident after initiation of HD therapy. To overcome the statistical error due to patients' variance we compared the survival of 20 HD patients without PHT who matched the group of patients with PHT incident after initiation of HD therapy in their age, gender, etiology of kidney disease, location of A-V access, and co-morbidities.

The association between clinical and hemodynamic variables and mortality was first evaluated using a uni-variable Cox proportional hazards model. The variables analyzed were predictors of adverse outcome from the literature, such as age, gender, etiology of ESRD, duration of HD therapy, A-V access location, co-morbid diseases, parameters of cardiac status (ischemic heart disease, significant valvular abnormalities, left ventricular dysfunction), presence and severity of PHT, and timing of PHT onset (before or incident after initiation of HD therapy). Thereafter, the Cox proportional hazards model was applied for the

multi-variant regressions of the variables found to be associated with death in the uni-variable model at the $P<0.1$ level. The HR for death and a 95% confidence interval were calculated. Differences were considered statistically significant at the two-sided $P<0.05$ level. Statistical analyses were carried out using the SPSS statistical package (Version 15.0).

DISCLOSURE

The authors declared no competing interests.

REFERENCES

1. Yigla M, Nakhoul F, Sabag A *et al.* Pulmonary hypertension in end-stage renal disease patients. *Chest* 2003; **123**: 1577–1582.
2. Nakhoul F, Yigla M, Gelman R *et al.* The pathogenesis of pulmonary hypertension in hemodialysis patients via arterial–venous access. *Nephrol Dial Transplant* 2005; **20**: 1686–1692.
3. Yigla M, Keidar Z, Safadi I *et al.* Pulmonary calcification in hemo-dialysis patients: correlation with pulmonary artery pressure values. *Kidney Int* 2004; **66**: 806–810.
4. Yigla M, Abassi Z, Reisner SA *et al.* Pulmonary hypertension in hemodialysis patients: an unrecognized threat. *Semin Dial* 2006; **19**: 353–357.
5. Abassi Z, Nakhoul F, Khankin E *et al.* Pulmonary hypertension in chronic dialysis patients with arteriovenous fistula: pathogenesis and therapeutic prospective. *Curr Opin Nephrol Hypertens* 2006; **15**: 353–360.
6. Yigla M, Banderski R, Azzam Z *et al.* Development of pulmonary hypertension after arterio–venous access formation among end-stage renal disease patients. *J Therapeutic Adv Respir Dis* 2008; **2**: 49–53.
7. Goldwasser P, Mittman N, Antignani A *et al.* Predictors of mortality in hemodialysis patients. *J Am Soc Nephrol* 1993; **3**: 1613–1622.
8. Ataga KI, Moore CG, Jones S *et al.* Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. *Br J Haematol* 2006; **134**: 109–115.
9. Proudman SM, Stevens WM, Sahhar J *et al.* Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. *Intern Med J* 2007; **37**: 485–494.
10. Villar E, Remontet L, Labeeuw M *et al.* Effect of age, gender, and diabetes on excess death in end-stage renal failure. *J Am Soc Nephrol* 2007; **18**: 2125–2134.
11. Wolfe R, Ashby W, Milford E *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of first cadavaric transplantation. *N Engl J Med* 1999; **341**: 1725–1730.
12. Jaar BG, Coresh J, Plantinga LC *et al.* Comparing the risk for death with peritoneal dialysis and hemodialysis in a national cohort of patients with chronic kidney disease. *Ann Intern Med* 2005; **143**: 174–183.
13. Heath D. The pathology of human pulmonary hypertension. *Eur Respir Rev* 1993; **3**: 555–558.
14. Jeffery TK, Morrel LW. Molecular and cellular basis of pulmonary vascular remodeling in pulmonary hypertension. *Prog Cardiovasc Dis* 2002; **45**: 173–202.
15. Reisner SA, Azzam Z, Halmann M *et al.* Septal to free wall curvature ratio: a non-invasive index of pulmonary arterial pressure. *J Am Soc Echocardiogr* 1994; **7**: 27–35.
16. Ihlen H, Endresen K, Golf S *et al.* Cardiac stroke volume during exercise measured by Doppler echocardiography: comparison with the thermo-dilution technique and evaluation of reproducibility. *Br Heart J* 1987; **58**: 455–459.
17. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; **47**: 186–192.