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Original Research Article

Pulmonary Hypertension Among Patients with Chronic Kidney Disease on Maintenance Haemodialysis: A Hospital-Based Cross-Sectional Study

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Abstract

Background: Pulmonary hypertension (PH) is an increasingly recognised cardiovascular complication of end-stage renal disease and an independent determinant of mortality. Data from Indian haemodialysis cohorts, particularly on the relationship between dialysis vintage and pulmonary arterial pressure, remain limited.

Objectives: To determine the prevalence and severity of PH by two-dimensional echocardiography among patients with chronic kidney disease (CKD) on maintenance haemodialysis (MHD), and to evaluate its association with duration of haemodialysis and selected clinical and biochemical variables.

Methods: This hospital-based cross-sectional study enrolled 70 adults with CKD on MHD for more than three months at hospitals attached to a tertiary care teaching institute. Patients with valvular, congenital, obstructive or restrictive pulmonary, thromboembolic or connective tissue disease, and those with PH antedating dialysis, were excluded. Pulmonary artery systolic pressure (PASP) was derived from peak tricuspid regurgitant velocity using the simplified Bernoulli equation; PASP greater than 40 mmHg defined PH. Groups were compared using the Chi-square test, independent samples t-test and Pearson correlation, with p less than 0.05 considered significant.

Results: PH was present in 37 of 70 patients (52.86%); 9 (12.86%) mild, 25 (35.71%) moderate and 3 (4.29%) severe. Mean PASP was 48 mmHg. Mean dialysis vintage was significantly longer in patients with PH than without (22 ± 16 versus 9 ± 4 months, $p = 0.001$), and PASP correlated positively with dialysis duration ($r = 0.462$, $p = 0.001$). Age, sex, aetiology of CKD, haemoglobin, calcium, phosphate, albumin, urea, creatinine and ejection fraction did not differ significantly between groups.

Conclusion: PH is highly prevalent in CKD patients on MHD and its occurrence and severity track with dialysis vintage, supporting routine echocardiographic surveillance.

Keywords: Chronic kidney disease; End-stage renal disease; Haemodialysis; Pulmonary hypertension; Echocardiography; Pulmonary artery systolic pressure.

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Introduction

Chronic kidney disease (CKD) has moved from the periphery to the centre of the global non-communicable disease agenda over the past two decades. The Global Burden of Disease Chronic Kidney Disease Collaboration analysed data from 195 countries for the period 1990 to 2017 and demonstrated that CKD is now a leading contributor to global mortality and disability, with the burden falling disproportionately on countries in the low and middle socio-demographic index quintiles.[1] In 2017 the global prevalence of CKD was estimated at 9.1%, corresponding to approximately 700 million prevalent cases, and the age-standardised incidence of end-stage kidney disease treated with renal replacement therapy rose by more than 40% over the study period.[2] These figures matter for the practising physician in two distinct ways. First, they signal that the population of patients surviving on maintenance haemodialysis (MHD) is expanding rapidly. Second, they imply that the complications that accumulate with dialysis vintage, rather than the complications of uraemia at presentation, will increasingly define the clinical workload of nephrology and general medicine services. Cardiovascular disease is the dominant cause of morbidity and mortality across the CKD spectrum, and the risk is not explained by traditional Framingham variables alone. Uraemia-specific mechanisms including chronic volume overload, endothelial dysfunction, accelerated

vascular and valvular calcification, mineral-bone disorder, anaemia, chronic low-grade inflammation and repeated haemodynamic stress during dialysis sessions all contribute. Within this constellation, pulmonary hypertension (PH) has emerged as a distinct and clinically consequential entity rather than an incidental echocardiographic finding.[3] Sise and colleagues, in a comprehensive review of PH across the spectrum of kidney disease, emphasised the substantial epidemiological overlap between kidney disease and the underlying causes of World Health Organization groups 1 to 4 PH, and argued that PH in CKD is frequently multifactorial rather than attributable to a single mechanism.[3]

Haemodynamically, PH is defined by an elevated mean pulmonary artery pressure measured at right heart catheterisation. Historically the threshold was set at 25 mmHg at rest; contemporary guidance has revised this downward to a mean pulmonary artery pressure above 20 mmHg, reflecting evidence that pressures in the 21 to 24 mmHg range already carry prognostic significance. Right heart catheterisation remains the diagnostic gold standard and is the only method that reliably separates pre-capillary from post-capillary disease through measurement of pulmonary artery wedge pressure and pulmonary vascular resistance.[8] In practice, however, catheterisation is invasive, resource-intensive and rarely justifiable as a screening tool in a dialysis population in whom vascular access preservation is itself a clinical priority. Two-dimensional Doppler echocardiography, which estimates pulmonary artery systolic pressure (PASP) from the peak tricuspid regurgitant jet velocity using the simplified Bernoulli equation with an added estimate of right atrial pressure, is therefore the accepted first-line screening modality in this population and the method on which the great majority of the published prevalence literature rests. [6,8]

Estimates of PH prevalence in dialysis populations vary widely, and this variability is itself informative. Reported figures range from below 10% to above 70%, driven by differences in the PASP threshold applied, the timing of echocardiography relative to the dialysis session, the rigour with which secondary causes are excluded, and the case mix of the dialysis unit. Two systematic reviews have attempted to impose order on this heterogeneity. Schoenberg and colleagues pooled data on prevalence and mortality in end-stage renal disease and confirmed both a high pooled prevalence and a consistent adverse survival signal.[5] Tang and colleagues, in a systematic review and meta-analysis of PH, mortality and cardiovascular disease across CKD and end-stage renal disease, found that PH was associated with a substantially increased risk of all-cause mortality and cardiovascular events, and that the association persisted after adjustment for conventional confounders. [4] Bolignano and co-workers reached a similar conclusion in an earlier synthesis, noting that PH in CKD is common, under-recognised and prognostically important, and that it is frequently overlooked because its symptoms overlap almost completely with those attributed to uraemia and volume overload.[6] The clinical corollary is uncomfortable: breathlessness and fatigue in a dialysis patient are so easily ascribed to interdialytic weight gain or anaemia that the diagnosis of PH is rarely entertained unless it is actively sought.

The importance of PH is not confined to patients already established on dialysis. In the Chronic Renal Insufficiency Cohort, Navaneethan and colleagues examined the prevalence, predictors and outcomes of PH in a large, well-characterised, non-dialysis CKD population and demonstrated that elevated PASP was present at earlier stages of CKD than had been assumed, and that it independently predicted adverse cardiovascular outcomes and progression to kidney failure.[9] This finding reframes PH as a marker of cumulative cardiopulmonary injury that begins before renal replacement therapy and accelerates thereafter, rather than as a purely dialysis-induced phenomenon.

The pathogenesis of PH in end-stage renal disease is best understood as the convergence of several partially independent mechanisms. The seminal observation by Yigla and colleagues, who described unexplained PH in patients on chronic haemodialysis in whom conventional causes had been systematically excluded, drew attention to the dialysis circuit itself as a candidate contributor.[10] The arteriovenous fistula, created deliberately to permit adequate extracorporeal blood flow, imposes a chronic high-output state: systemic vascular resistance falls, venous return rises and cardiac output increases, and this augmented flow must be accommodated by the pulmonary vascular bed. Nakhoul and colleagues examined this pathway directly and proposed that the failure of the pulmonary circulation to adapt to sustained high flow, in the setting of uraemic endothelial dysfunction and impaired nitric oxide bioavailability, is central to the development of PH in patients dialysed through arteriovenous access.[11] Supporting this, PH has been reported to regress after fistula ligation and after successful renal transplantation. A second mechanism relates to mineral-bone disorder. Akmal and colleagues demonstrated in an experimental model of chronic renal failure that excess parathyroid hormone induces pulmonary calcification, pulmonary hypertension and right ventricular hypertrophy, and that parathyroidectomy attenuated these changes.[12] Metastatic calcification of the pulmonary vasculature is common at autopsy in

end-stage renal disease yet is seldom apparent on plain chest radiography, which may explain why this mechanism is under-appreciated at the bedside. A third mechanism is chronic inflammation. Yu and colleagues showed that systemic inflammatory activation is associated with PH in patients undergoing haemodialysis, consistent with a model in which circulating cytokines and uraemic toxins drive pulmonary vascular remodelling over time.[13] Chronic volume overload, anaemia with compensatory high cardiac output, left ventricular diastolic dysfunction producing post-capillary pulmonary venous hypertension, dialysis membrane bio-incompatibility and recurrent subclinical thromboembolism from access thrombosis have all been implicated as additional contributors.[3, 7]

What unites most of these mechanisms is that they are cumulative. Fistula flow, calcification burden, inflammatory exposure and left ventricular remodelling all increase with time on dialysis. If this reasoning is correct, dialysis vintage should behave as a proxy variable for total cardiopulmonary injury, and the prevalence and severity of PH should rise as duration of MHD increases. Testing this relationship in a defined cohort has direct practical value, because dialysis vintage is a variable that is known for every patient without additional cost or investigation, and could therefore be used to prioritise echocardiographic screening in resource-constrained units.

The consequences of missing the diagnosis are not trivial. Yigla and colleagues subsequently demonstrated that PH is an independent predictor of mortality in haemodialysis patients, and PH is also associated with early allograft dysfunction and reduced patient survival after renal transplantation, to the extent that significant PH is generally regarded as a relative contraindication to transplantation.[14] Devasahayam and colleagues, reviewing PH in end-stage renal disease, stressed that recognition alters management in concrete ways: intensified volume control and lowering of target dry weight, reconsideration of access flow with flow-reduction procedures or ligation where indicated, preference for peritoneal dialysis or tunnelled catheter access in selected patients, and, in a minority, the use of pulmonary vasodilator therapy under specialist supervision.[7] Indian data on this question remain comparatively sparse.

Mehta and colleagues studied 200 CKD patients across stages and reported a prevalence of PH of 60.5% with a mean PASP of 38.52 ± 7.32 mmHg, and found that both the prevalence and the severity of PH correlated with the duration of CKD, the presence of haemodialysis and the presence of an arteriovenous fistula.[15] Beyond this and a small number of comparable series, there is limited prospectively collected Indian evidence describing PH specifically within the MHD subgroup, and less still that quantifies the relationship between dialysis vintage and PASP as a continuous variable.

The present study was therefore undertaken to determine the prevalence and severity of PH, assessed by two-dimensional echocardiography, among patients with CKD on MHD at a tertiary care teaching hospital, and to examine its association with duration of haemodialysis and with the demographic, echocardiographic and biochemical variables routinely available in this population. The intention was to generate locally applicable data that could inform screening practice and identify the subgroup of dialysis patients in whom the yield of echocardiographic surveillance is likely to be highest.

Aims and Objectives

Aim: To evaluate pulmonary hypertension in patients with chronic kidney disease on maintenance haemodialysis and to define its relationship with duration of haemodialysis.

Primary objectives

1. To evaluate the presence and severity of pulmonary hypertension, assessed by two-dimensional echocardiography, in patients with chronic kidney disease on maintenance haemodialysis.
2. To evaluate the association between the presence of pulmonary hypertension and the duration of haemodialysis.

Secondary Objective: To compare demographic characteristics, aetiology of chronic kidney disease, left ventricular ejection fraction and biochemical parameters (haemoglobin, serum calcium, serum phosphate, serum albumin, blood urea and serum creatinine) between patients with and without pulmonary hypertension.

Materials and Methods

Study Design and Setting: This was a hospital-based, observational, cross-sectional study conducted in the Department of General Medicine at hospitals attached to a tertiary care teaching institute. Patients were recruited from both the medical outpatient department and the inpatient wards, together with the attached haemodialysis unit.

Study Period: The study was conducted between February 2021 and August 2022.

Ethical Considerations: The study protocol was reviewed and approved by the Institutional Ethics Committee before commencement of recruitment. Written informed consent was obtained from every participant in a language they understood, after the purpose, procedures, potential risks and benefits of the study had been explained.

Participants were informed that participation was entirely voluntary, that they could withdraw at any stage without assigning a reason, and that withdrawal would not affect the clinical care they received. All data were anonymised and handled in confidence and were used solely for the stated scientific purpose. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population and Sampling: Consecutive patients with CKD receiving MHD who fulfilled the eligibility criteria and consented to participate were enrolled until the calculated sample size was achieved.

Inclusion Criteria

Patients were eligible if they satisfied all of the following:

1. Age greater than 18 years.
2. A diagnosis of CKD established according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria, that is, abnormalities of kidney structure or function present for more than three months, comprising either one or more markers of kidney damage (albuminuria with an albumin excretion rate of 30 mg per 24 hours or more, urine sediment abnormalities, electrolyte or other abnormalities attributable to tubular disorders, histological abnormalities, structural abnormalities on imaging, or a history of kidney transplantation) or a glomerular filtration rate below 60 mL/min/1.73 m^2.
3. Receipt of maintenance haemodialysis for a period exceeding three months.
4. Provision of written informed consent.

Exclusion Criteria

Patients were excluded if any of the following were present, since each constitutes an alternative cause of pulmonary hypertension:

1. Refusal or inability to provide informed consent.
2. Age below 18 years.
3. Clinical history and examination suggestive of valvular heart disease.
4. Clinical history and examination suggestive of congenital heart disease.
5. Clinical history and examination suggestive of obstructive or restrictive pulmonary disease.
6. Clinical history and examination suggestive of thromboembolic disorders.
7. Clinical history and examination suggestive of connective tissue disease.
8. A documented history of pulmonary hypertension antedating the initiation of haemodialysis therapy.

Sample Size Estimation: The sample size was calculated using the formula for estimation of a single proportion, $n = 4pq/d^2$, where p was the expected prevalence of pulmonary hypertension, q was 100 minus p and d was the absolute precision. Taking the prevalence of pulmonary hypertension among haemodialysis patients as 34% from a previously published Indian cross-sectional study,[18] and setting absolute precision at 12%, the calculation yielded $n = (4 \times 34 \times 66)/144 = 62.3$. The minimum required sample size was therefore 62, which was rounded upward to 70 to allow for incomplete data.

Data Collection: A structured, pre-tested study proforma was used for all participants. A detailed clinical history was obtained, covering the time of diagnosis of CKD, the underlying aetiology where known, the duration and frequency of haemodialysis, the type of arteriovenous access, comorbid conditions, past history, family history, personal and substance-use history, and symptoms attributable to pulmonary hypertension.

A complete general physical examination was performed, including assessment of build and nutritional status with height, weight and body mass index, oral cavity, pallor, icterus, cyanosis, clubbing, lymphadenopathy, pedal oedema and skin changes, together with recording of pulse rate, blood pressure, respiratory rate and temperature.

Systemic examination of the respiratory, cardiovascular, abdominal and nervous systems was carried out in every patient.

Dialysis Prescription: All 70 patients were dialysed through an arteriovenous fistula, receiving three sessions per week, each of four hours duration. Uniformity of the dialysis prescription across the cohort removed session frequency and session duration as sources of variation between the groups compared.

Laboratory Investigations: Venous blood samples were drawn for estimation of haemoglobin, blood urea, serum creatinine, serum calcium, serum phosphate and serum albumin. Samples were processed in the institutional central laboratory using standard automated methods.

Echocardiographic Assessment: Two-dimensional transthoracic echocardiography was performed in every patient by an operator blinded to the biochemical results. Standard transducer positions were used.

Pulmonary artery systolic pressure was calculated using the simplified Bernoulli equation applied to the peak tricuspid regurgitant velocity, with the addition of an estimate of right atrial pressure, according to the formula: systolic pulmonary artery pressure = right ventricular systolic pressure = $4 \times (\text{peak tricuspid regurgitant velocity})^2$ + estimated right atrial pressure. Left ventricular ejection fraction was recorded in the same sitting.

Operational Definitions: Pulmonary hypertension was defined as a pulmonary artery systolic pressure greater than 40 mmHg on two-dimensional echocardiography. Patients with pulmonary hypertension were further stratified into mild, moderate and severe categories on the basis of the pre-specified PASP strata used in the study protocol.

Statistical Analysis: Data were entered into a Microsoft Excel spreadsheet and analysed using SPSS version 20 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages, and continuous variables as mean and standard deviation. Comparison of categorical variables between patients with and without pulmonary hypertension was performed using the Chi-square test, with Fisher exact test applied where expected cell counts were small. Continuous variables were compared using the independent samples t-test, and comparison across the four severity strata was performed using analysis of variance. The relationship between pulmonary artery systolic pressure and duration of haemodialysis was assessed using the Pearson correlation coefficient. A two-tailed p value below 0.05 was considered statistically significant. Results were presented in tabular and graphical form.

Results

Seventy patients with chronic kidney disease on maintenance haemodialysis were enrolled and analysed. All were dialysed via an arteriovenous fistula three times weekly for four hours per session.

Demographic Profile: The largest single age band was 40 to 49 years, which accounted for 19 patients (27.14%) (Table 1). The mean age of the cohort was 47 years, with the youngest participant aged 20 years and the oldest 76 years. Fifty-two patients (74.29%) were male and 18 (25.71%) were female, giving a male to female ratio of 2.9 to 1.

Table 1: Distribution of the study population by age group and sex (n = 70)

Variable	Category	Number of patients	Percentage
Age group (years)	20 to 29	11	15.71
	30 to 39	12	17.14
	40 to 49	19	27.14
	50 to 59	10	14.29
	60 to 69	14	20.00
	70 to 80	4	5.71
Sex	Male	52	74.29
	Female	18	25.71
Total		70	100.00

Mean age 47 years; range 20 to 76 years; male to female ratio 2.9 to 1.

Aetiology of chronic kidney disease and dialysis vintage: Diabetic kidney disease was the commonest underlying cause, present in 31 patients (44.29%), followed by chronic interstitial nephritis in 20 (28.57%), chronic glomerulonephritis in 14 (20.00%) and IgA nephropathy in 5 (7.14%) (Table 2). The largest group by dialysis vintage was 7 to 12 months, comprising 29 patients (41.43%). The mean duration of haemodialysis for the cohort was 16 months.

Table 2: Aetiology of chronic kidney disease and duration of maintenance haemodialysis (n = 70)

Variable	Category	Number of patients	Percentage
Aetiology of CKD	Diabetic kidney disease	31	44.29
	Chronic interstitial nephritis	20	28.57
	Chronic glomerulonephritis	14	20.00
	IgA nephropathy	5	7.14
Duration of haemodialysis (months)	1 to 6	13	18.57
	7 to 12	29	41.43
	13 to 18	17	24.29
	31 to 36	6	8.57
	43 to 48	2	2.86
	49 to 54	1	1.43
	55 to 60	2	2.86
Total		70	100.00

CKD, chronic kidney disease. Mean duration of haemodialysis 16 months.

Prevalence and severity of pulmonary hypertension: Pulmonary hypertension was detected in 37 of the 70 patients, giving a prevalence of 52.86%, while 33 patients (47.14%)

had normal pulmonary artery systolic pressures. The mean PASP for the cohort was 48 mmHg. Among the 37 patients with pulmonary hypertension, moderate disease predominated, affecting 25 patients (67.57% of those with pulmonary hypertension and 35.71% of the total cohort). Mild pulmonary hypertension was present in 9 patients (24.32% of those affected) and severe pulmonary hypertension in 3 patients (8.11% of those affected) (Table 3).

Table 3: Prevalence and severity of pulmonary hypertension (n = 70)

Category	Number of patients	Percentage of total cohort	Percentage of patients with PH
Pulmonary hypertension absent	33	47.14	-
Pulmonary hypertension present	37	52.86	100.00
Mild	9	12.86	24.32
Moderate	25	35.71	67.57
Severe	3	4.29	8.11
Total	70	100.00	-

PH, pulmonary hypertension. Mean pulmonary artery systolic pressure 48 mmHg.

Demographic and aetiological variables in relation to pulmonary hypertension: No statistically significant association was demonstrated between pulmonary hypertension and age, sex or the underlying aetiology of chronic kidney disease (Table 4). The mean age of patients with pulmonary hypertension was 45 ± 15 years compared with 50 ± 15 years in those without, a difference that did not reach statistical significance (p = 0.635). Pulmonary hypertension was present in 28 of 52 male patients (53.85%) and 9 of 18 female patients (50.00%), with a p value of 0.700. Across the four aetiological categories, the proportion of patients affected ranged from 42.86% in chronic glomerulonephritis to 80.00% in IgA nephropathy, but the overall comparison was not statistically significant (p = 0.541), a finding that should be interpreted with caution given the very small number of patients in the IgA nephropathy category.

Table 4: Demographic and aetiological characteristics in patients with and without pulmonary hypertension (n = 70)

Variable	Category	PH absent (n = 33)	PH present (n = 37)	Total (n = 70)	p value
Age (years)	Mean ± SD	50 ± 15	45 ± 15	48 ± 15	0.635
Age group	20 to 29	4 (12.12)	7 (18.92)	11 (15.71)	-
	30 to 39	5 (15.15)	7 (18.92)	12 (17.14)	-
	40 to 49	10 (30.30)	9 (24.32)	19 (27.14)	-
	50 to 59	1 (3.03)	9 (24.32)	10 (14.29)	-
	60 to 69	11 (33.33)	3 (8.11)	14 (20.00)	-
	70 to 80	2 (6.06)	2 (5.41)	4 (5.71)	-
Sex	Male	24 (72.70)	28 (75.70)	52 (74.30)	0.700
	Female	9 (27.30)	9 (24.30)	18 (25.70)	
Aetiology of CKD	Chronic glomerulonephritis	8 (24.20)	6 (16.20)	14 (20.00)	0.541
	Chronic interstitial nephritis	10 (30.30)	10 (27.00)	20 (28.60)	
	Diabetic kidney disease	14 (42.40)	17 (45.90)	31 (44.30)	
	IgA nephropathy	1 (3.00)	4 (10.80)	5 (7.10)	

Values are n (%) unless otherwise stated. PH, pulmonary hypertension; SD, standard deviation; CKD, chronic kidney disease.

Duration of haemodialysis and pulmonary hypertension: The relationship between dialysis vintage and pulmonary hypertension was the most robust finding of the study (Table 5). The mean duration of haemodialysis was 22 ± 16 months in patients with pulmonary hypertension compared with 9 ± 4 months in those without, and this difference was highly statistically significant (p = 0.001). When the cohort was stratified by severity, the mean dialysis vintage was 9 ± 4 months in patients without pulmonary hypertension, 20 ± 19 months in those with mild disease, 24 ± 15 months in those with moderate disease and 12 ± 4 months in those with severe disease, with an overall p value of 0.001. Pearson correlation analysis demonstrated a statistically significant moderate positive correlation between pulmonary artery systolic pressure and duration of dialysis, with a correlation coefficient of 0.462 and a p value of 0.001, indicating that patients with longer dialysis vintage recorded higher PASP values.

Table 5: Duration of haemodialysis in relation to presence, severity and magnitude of pulmonary hypertension (n = 70)

Comparison	Group	Mean duration of HD (months) ± SD	p value
By presence of PH	PH absent (n = 33)	9 ± 4	0.001
	PH present (n = 37)	22 ± 16	
	Total (n = 70)	16 ± 13	
By severity of PH	No PH (n = 33)	9 ± 4	0.001
	Mild (n = 9)	20 ± 19	
	Moderate (n = 25)	24 ± 15	
	Severe (n = 3)	12 ± 4	
Correlation	PASP versus duration of HD	Pearson r = 0.462	0.001

HD, haemodialysis; PH, pulmonary hypertension; PASP, pulmonary artery systolic pressure; SD, standard deviation.

Biochemical and echocardiographic parameters: None of the biochemical parameters examined, nor left ventricular ejection fraction, differed significantly between patients with and without pulmonary hypertension (Table 6). Mean haemoglobin was 9.3 ± 1.7 g/dL in the pulmonary hypertension group and 9.0 ± 1.5 g/dL in those without (p = 0.152). Mean serum phosphate was 4.03 ± 1.14 mg/dL versus 4.32 ± 1.11 mg/dL (p = 0.452) and mean serum calcium was 8.12 ± 0.6 mg/dL versus 7.93 ± 0.6 mg/dL (p = 0.685). Mean serum albumin was 3.6 ± 0.6 g/dL in patients with pulmonary hypertension and 3.3 ± 0.5 g/dL in those without (p = 0.142). Mean blood urea was 91.4 ± 22.6 mg/dL versus 86.2 ± 24.4 mg/dL (p = 0.459) and mean serum creatinine was 5.2 ± 1.6 mg/dL versus 5.3 ± 1.5 mg/dL (p = 0.964).

Mean left ventricular ejection fraction was 55 ± 9% in patients with pulmonary hypertension and 56 ± 8% in those without (p = 0.635); all patients therefore had preserved systolic function, which is relevant to the interpretation of the pulmonary pressures recorded.

Table 6: Biochemical and echocardiographic parameters in patients with and without pulmonary hypertension (n = 70)

Parameter	PH absent (n = 33)	PH present (n = 37)	Total (n = 70)	p value
Haemoglobin (g/dL)	9.0 ± 1.5	9.3 ± 1.7	9.2 ± 1.6	0.152
Serum phosphate (mg/dL)	4.32 ± 1.11	4.03 ± 1.14	4.16 ± 1.13	0.452
Serum calcium (mg/dL)	7.93 ± 0.6	8.12 ± 0.6	8.03 ± 0.6	0.685
Serum albumin (g/dL)	3.3 ± 0.5	3.6 ± 0.6	3.5 ± 0.6	0.142
Blood urea (mg/dL)	86.2 ± 24.4	91.4 ± 22.6	88.9 ± 23.5	0.459
Serum creatinine (mg/dL)	5.3 ± 1.5	5.2 ± 1.6	5.2 ± 1.5	0.964
Left ventricular ejection fraction (%)	56 ± 8	55 ± 9	55 ± 9	0.635

Values are mean ± standard deviation. PH, pulmonary hypertension.

Discussion

The central findings of this study are that pulmonary hypertension affected more than half of an unselected cohort of patients with chronic kidney disease on maintenance haemodialysis, that its occurrence and its magnitude were strongly related to the duration of dialysis, and that none of the demographic or biochemical variables routinely measured in this population distinguished patients with pulmonary hypertension from those without.

Prevalence: The observed prevalence of 52.86% sits within the upper half of the range reported in the literature but is by no means exceptional. Schoenberg and colleagues, in a systematic review and meta-analysis of prevalence and mortality in end-stage renal disease, confirmed a pooled prevalence in this range together with a consistent adverse mortality signal.[5] A subsequent large meta-analysis synthesising fifty observational studies comprising 17,558 patients reported a pooled prevalence of pulmonary hypertension of 38% across the whole CKD spectrum, rising to 42% (95% confidence interval 35% to 50%) among patients on haemodialysis specifically.[4,5] Our figure exceeds this pooled estimate, and the most probable explanations are the exclusive recruitment of patients dialysed via arteriovenous fistula, all of whom therefore carried a chronic high-output haemodynamic burden, and the relatively high proportion of patients with diabetic kidney disease.

Indian series report broadly comparable or higher figures. Suresh and colleagues, in a prospective study of 108 CKD patients at a Karnataka tertiary centre, found pulmonary hypertension in 47 patients, a prevalence of 43.5%, and identified it as a new and prognostically important complication of CKD.[16] Mehta and colleagues reported a prevalence of 60.5% among 200 Indian CKD

patients with a mean PASP of 38.52 ± 7.32 mmHg, noting that prevalence correlated positively with CKD stage, duration of CKD, receipt of haemodialysis and the presence of an arteriovenous fistula.[15] Nithiya and colleagues studied 113 adult CKD patients and likewise reported a high prevalence with an association with vascular calcification.[17] Singh and colleagues, whose reported prevalence of 34% provided the basis for our sample size calculation, examined patients with end-stage renal disease on maintenance haemodialysis in a cross-sectional design.[18] The lower figure in that series may reflect differences in the PASP threshold applied and in the timing of echocardiography relative to dialysis. Our finding is also consistent with data from outside India: Mukhtar and colleagues reported a high frequency among 80 haemodialysis patients in Karachi,[24] and Khemchandani and colleagues, studying 220 patients on maintenance haemodialysis, found an average pulmonary artery pressure of 35.2 ± 15.3 mmHg with mild pulmonary hypertension in 49.8%, moderate in 32.7% and severe in 4.1%.[25]

The distribution of severity in our cohort, with moderate disease predominating at 67.57% of affected patients and severe disease confined to 8.11%, differs from that of Khemchandani and colleagues, in whose series mild disease predominated.[25] This difference almost certainly reflects the differing PASP cut-offs used to define the severity bands rather than a genuine difference in disease burden, and underlines the need for standardised severity thresholds in this literature. Notably, the proportion with severe disease was low in both series.

Dialysis Vintage: The strongest and most consistent signal in our data was the association with duration of haemodialysis. Mean vintage was more than twice as long in patients with pulmonary hypertension (22 ± 16 versus 9 ± 4 months, $p = 0.001$), and PASP correlated positively with duration of dialysis ($r = 0.462$, $p = 0.001$). This accords closely with the published evidence. Mehta and colleagues found that the severity of pulmonary hypertension was directly proportional to both the duration of CKD and the duration of haemodialysis.[15] Tudoran and colleagues, studying patients with end-stage renal disease undergoing haemodialysis, similarly demonstrated a positive relationship between prevalence and dialysis duration.[20] Afzal and colleagues reported that the prevalence of pulmonary hypertension increased significantly as dialysis duration increased.[21] At the level of pooled evidence, the meta-analysis of predictors across fifty studies identified longer dialysis duration as an independent risk factor for pulmonary hypertension, with a relative risk of 1.70 (95% confidence interval 1.18 to 2.46, $p = 0.005$).[4]

The mechanistic reading of this finding is that dialysis vintage functions as a surrogate for cumulative cardiopulmonary injury. Time on dialysis integrates the total duration of exposure to high fistula flow, to uraemic endothelial dysfunction, to inflammatory activation and to progressive vascular calcification. Nakhoul and colleagues argued specifically that sustained augmentation of cardiac output through arteriovenous access, in the presence of a pulmonary vascular bed rendered less compliant by uraemia, is a primary driver of pulmonary hypertension in this population.[11] Yu and colleagues demonstrated the parallel contribution of systemic inflammation,[13] and Akmal and colleagues, along with Amin and colleagues, established the contribution of excess parathyroid hormone and pulmonary artery calcification.[12,28] Each of these exposures accumulates over time, which explains why vintage rather than any single cross-sectional biochemical measurement was the discriminating variable in our cohort.

One apparently discordant observation deserves comment. Mean dialysis vintage in patients with severe pulmonary hypertension was 12 ± 4 months, lower than in the mild and moderate groups. This should not be over-interpreted: only three patients had severe disease, and an estimate derived from three observations carries very wide uncertainty. It is also plausible that patients who develop severe pulmonary hypertension early represent a phenotype driven by dominant volume overload or by very high access flow rather than by cumulative exposure, and that survivorship effects operate at longer vintages. The overall gradient across the no-pulmonary-hypertension, mild and moderate strata remains monotonic and significant.

Demographic Variables: We found no significant association between pulmonary hypertension and age ($p = 0.635$) or sex ($p = 0.700$). Singh and colleagues reported an almost identical absence of an age effect, with mean ages of 47.2 years in the group with pulmonary hypertension and 50.79 years in the group without.[18] Zhang and colleagues, in a retrospective analysis of 491 patients with end-stage renal disease on maintenance dialysis, likewise did not identify age or sex as discriminating variables.[19] The literature is not entirely uniform on sex: Mehta and colleagues found pulmonary hypertension to be significantly more common in males ($p = 0.03$),[15] whereas our data showed almost identical proportions in the two sexes (53.85% of males and 50.00% of females). The male preponderance of our cohort overall, at 74.29%, reflects the established sex distribution of patients accessing maintenance dialysis in India rather than any biological susceptibility to pulmonary hypertension.

Aetiology of chronic kidney disease: The aetiological comparison was not statistically significant in our cohort (p = 0.541), which is consistent with the majority of published series. Zhang and colleagues found no significant difference in the prevalence of pulmonary hypertension across native kidney diseases,[19] as did Zhang and co-workers in a separate retrospective analysis of 705 CKD patients using a PASP threshold of 35 mmHg.[23] Tudoran and colleagues, by contrast, reported a significant association between chronic glomerulonephritis and pulmonary hypertension.[20] The most likely explanation for our null result is limited statistical power: with only five patients in the IgA nephropathy category, the study was not designed to detect aetiology-specific effects, and the numerically high proportion affected in that subgroup (4 of 5) should be regarded as a chance finding.

Biochemical and Echocardiographic Parameters: The uniformly non-significant biochemical comparisons in our data merit emphasis rather than dismissal. Haemoglobin did not differ between groups (9.3 ± 1.7 versus 9.0 ± 1.5 g/dL, p = 0.152), replicating almost exactly the finding of Singh and colleagues, who reported haemoglobin values of 9.22 ± 1.42 and 9.45 ± 1.62 g/dL in the two groups with a p value of 0.511.[18] Serum calcium (p = 0.685) and phosphate (p = 0.452) did not differ, in keeping with the findings of Zhang and colleagues,[19] although Mehta and colleagues did find a significantly higher calcium-phosphorus product among CKD patients with pulmonary hypertension, [15] suggesting that the derived product may be a more sensitive index of calcification burden than either constituent measured alone. Serum albumin (p = 0.142), urea (p = 0.459) and creatinine (p = 0.964) were likewise non-discriminating. Ejection fraction was preserved and comparable in both groups (55 ± 9 versus 56 ± 8%, p = 0.635), which argues against left ventricular systolic dysfunction as the mechanism in this cohort and directs attention instead towards high-output physiology, diastolic dysfunction and pulmonary vascular remodelling. This inference aligns with the observations of Sonkar and colleagues, who identified volume status and inflammatory markers rather than conventional biochemistry as the variables associated with pulmonary hypertension in an Indian haemodialysis cohort,[26] and with those of Engole and colleagues in a Central African dialysis population.[27]

The practical message from this pattern is that no routinely available biochemical parameter reliably identifies which dialysis patient harbours pulmonary hypertension. Detection depends on echocardiography, and the variable that best predicts who should be screened is dialysis vintage. Pabst and colleagues reached a similar conclusion in the PEPPER study, in which the diagnosis in patients with and without dialysis rested on echocardiographic rather than clinical or laboratory criteria.[22]

Clinical Implications: Three implications follow. First, echocardiographic screening for pulmonary hypertension should be incorporated into the routine periodic assessment of patients on maintenance haemodialysis, with the interval shortened as dialysis vintage lengthens. Second, given the frequency with which the diagnosis is present in patients being evaluated for transplantation, and the association of pulmonary hypertension with early allograft dysfunction and reduced post-transplant survival, echocardiography should form part of the pre-transplant workup rather than being reserved for symptomatic patients.[14] Third, recognition changes management: aggressive volume control with a lower achievable dry weight, assessment of access flow with consideration of flow-reduction or ligation in patients with high-flow fistulae, consideration of peritoneal dialysis or tunnelled catheter access in selected patients, and, in refractory cases, referral for specialist assessment for pulmonary vasodilator therapy.[7,8]

Limitations: Several limitations should be acknowledged. The sample size of 70 was modest, and the study was consequently underpowered to detect aetiology-specific associations or to characterise the small severe pulmonary hypertension subgroup reliably. Pulmonary hypertension was diagnosed by echocardiography rather than by right heart catheterisation, which remains the gold standard and is the only method capable of distinguishing pre-capillary from post-capillary disease; echocardiographic PASP estimation is operator-dependent and load-dependent, and the volume status of a dialysis patient at the time of imaging materially influences the value obtained.

Serial echocardiography and longitudinal follow-up were not undertaken, so the temporal evolution of PASP within individual patients could not be described and causality cannot be inferred from a cross-sectional design. No pre-dialysis CKD comparison group was studied, which limits the ability to separate the contribution of dialysis itself from that of advanced uraemia. Parathyroid hormone, inflammatory markers and access flow rate, all mechanistically relevant, were not measured. Finally, the single-centre design limits generalisability.

Conclusion

Pulmonary hypertension was present in 52.86% of patients with chronic kidney disease receiving

maintenance haemodialysis in this cross-sectional study, with moderate disease predominating. Its presence and its magnitude were significantly associated with the duration of haemodialysis: mean dialysis vintage was 22 ± 16 months in patients with pulmonary hypertension compared with 9 ± 4 months in those without ($p = 0.001$), and pulmonary artery systolic pressure correlated positively with dialysis duration ($r = 0.462$, $p = 0.001$). Neither age, sex, aetiology of chronic kidney disease, haemoglobin, calcium, phosphate, albumin, urea, creatinine nor left ventricular ejection fraction differentiated the two groups, indicating that routinely measured demographic and biochemical variables cannot be relied upon to identify affected patients.

These findings support two conclusions of practical consequence. Pulmonary hypertension in this population appears to be driven predominantly by cumulative haemodynamic and vascular exposures that accrue with time on dialysis rather than by any single measurable metabolic derangement. And because clinical and laboratory assessment cannot substitute for imaging, all patients with end-stage renal disease on maintenance haemodialysis should undergo periodic echocardiographic screening for pulmonary hypertension, with particular attention to those with longer dialysis vintage and to those under evaluation for renal transplantation. Where pulmonary hypertension is identified, a systematic search for contributory and reversible causes should follow, encompassing volume status, arteriovenous access flow, left heart disease and sleep-disordered breathing, since early recognition and targeted intervention offer the prospect of reduced morbidity and improved quality of life. Larger prospective multicentre studies incorporating right heart catheterisation, serial echocardiography, access flow measurement and inflammatory and mineral-bone markers are needed to define the relative contribution of each pathogenic pathway and to establish evidence-based screening intervals.

Declarations

Ethics approval and consent to participate: Approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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