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ASSOCIATION OF FLUID OVERLOAD AND PULMONARY HYPERTENSION IN PATIENTS ON HEMODIALYSIS

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ABSTRACT

Background: The term "chronic kidney disease" (CKD) refers to abnormalities in kidney structure or function that have been present for three months or longer and have an impact on health. Pulmonary hypertension (PH) is a heterogeneous disease involving pathogenic remodeling of the pulmonary vasculature, which increases pulmonary artery pressure and vascular resistance. **Aim of the study:** To evaluate the effect of fluid overload on pulmonary hypertension in patients on hemodialysis. **Patients and methods:** This is a cross-sectional study that was conducted at the dialysis center of Baghdad Teaching Hospital - Medical City in collaboration with the dialysis department during the period from the 1st of December, 2024 to the 31st of May, 2025. In this study; 100 patients were included. **Results:** In the present study 100 patients were included, the mean age of presentation was 49.0 ± 12.5 (20-69) years, 73 of them were males and 27 were females. They were evaluated according to history of patients, clinical examination, laboratory findings, BCM assessment and Echo study. Pulmonary hypertension was found in 50% of them. **Conclusion:** The conclusion of this study is that there is direct effect of fluid overload in patients with end-stage renal disease, which leads to many clinical manifestations. Therefore, we recommend fluid restriction, avoid nephrotoxic drugs, good control of the risk factors, adherence to the sessions of dialysis with regular follow-up and assessment.

KEYWORDS: ESKD, Pulmonary hypertension and fluid overload.

INTRODUCTION

1.1 Chronic kidney disease

1.1.1 Definition

The term "chronic kidney disease" (CKD) refers to abnormalities in kidney structure or function that have been present for three months or longer and have an impact on health.[1]

Table 1-1: Criteria for chronic kidney disease.[1]

CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health. These may include the following:	
Markers of kidney damage	Albuminuria (AER ≥30 mg/24 h; uACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities caused by tubular disorders Abnormalities detected through histology Structural abnormalities detected through imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2

1.1.2 Risk factors

It is important to identify factors that increase the risk for CKD, even in individuals with normal GFR. Risk factors include: hypertension, diabetes mellitus, autoimmune disease, glomerulonephritis, Autosomal dominant polycystic kidney disease, advanced age, African ancestry, a family history of kidney disease, a previous episode of acute kidney injury, and the presence of proteinuria, abnormal urinary sediment, or structural abnormalities of the urinary tract and other cystic and tubulointerstitial nephropathy.[1]

1.1.3 Pathophysiology

The kidneys play a vital role in maintaining water balance through the regulation of water excretion. The ability to concentrate urine to an osmolality exceeding that of plasma allows water conservation, while the ability to produce urine more dilute than plasma promotes excretion of excess water.[1]

Homeostatic mechanisms that regulate the intake and excretion of water allow body fluids to remain tonic within a limited physiological range.

Vasopressin, also referred to as antidiuretic hormone (ADH) or arginine vasopressin (AVP), regulates water excretion through its impact on the renal collecting system. The hypothalamus contains osmo receptors that regulate the release of AVP in response to variations in tonicity.[2] Aquaporin must be expressed by the cell membrane for water to enter or leave a cell.

In the proximal and distal tubules of the kidney, aquaporin-1 is constitutively active, but aquaporin-2, -3, and -4 in the inner medullary collecting duct are controlled by vasopressin and facilitate fast water permeability. The osmotic gradient between a hypertonic medullary interstitium and a dilute tubular fluid eventually drives net water reabsorption. The pathophysiology of chronic kidney disease (CKD) involves two broad sets of mechanisms of damage:[1]

(1) Mechanisms specific to the underlying etiology, such as immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain diseases of the renal tubules and interstitium.
(2) A set of progressive mechanisms which, regardless of the underlying etiology, are a common consequence following long-term reduction of renal mass and involve hyperfiltration and hypertrophy of the remaining viable nephrons.

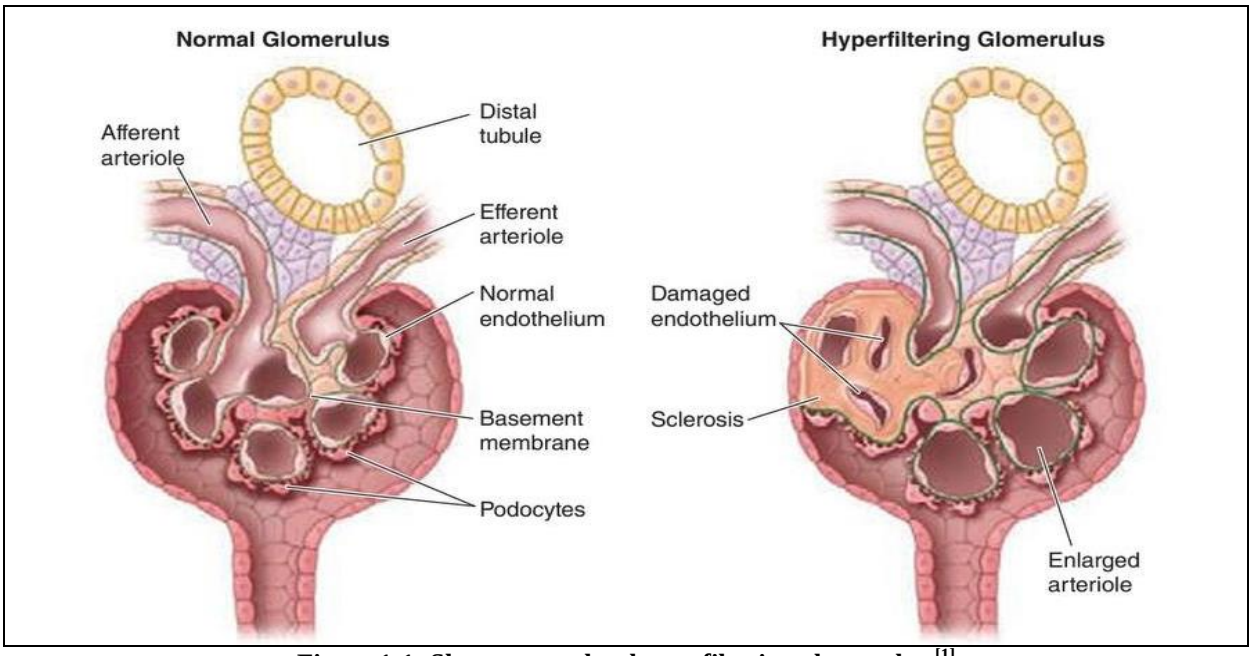


Figure 1-1: Shows normal vs hyper filtering glomerulus.[1]

1.1.4. Staging

Chronic Kidney Disease Staging Over the past decade, the definition of CKD has evolved to incorporate advances in knowledge about prognosis.[3] The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guidelines published in 2002 classified CKD into five stages on the basis of glomerular filtration rate (GFR) and signs of kidney damage (pathologic abnormalities or markers of damage in blood, urine, or imaging studies).[4] This staging system was modified in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines to reflect the independent contributions of GFR, albuminuria, and cause of CKD.[5] The two-dimensional "heat map" that classifies CKD in GFR categories (G stages) and albuminuria categories (A stages) has been widely accepted and robustly validated, but less is known about the third dimension, as routine reporting on the cause of CKD is relatively uncommon (Fig. 1-2).[6]

Table 1-2: Chronic kidney disease staging classification.[6]

GFR categories (mL/min/1.73 m²) description and range			Persistent albuminuria categories description and range		
G1	Normal or high	≥90	A1	A2	A3
G2	Mildly decreased	60-89	Normal to mildly increased	Moderately increased	Severely increased
G3a	Mildly to moderately decreased	45-59			
G3b	Moderately to severely decreased	30-44			
G4	Severely decreased	15-29	<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
G5	Kidney failure	<15			

Classification of CKD based on presence or absence of systemic disease and location within the kidney	
Presence of systemic disease affecting the kidney	Primary kidney diseases
Glomerular diseases	
Tubulointerstitial diseases	
Vascular diseases	
Cystic and congenital diseases	

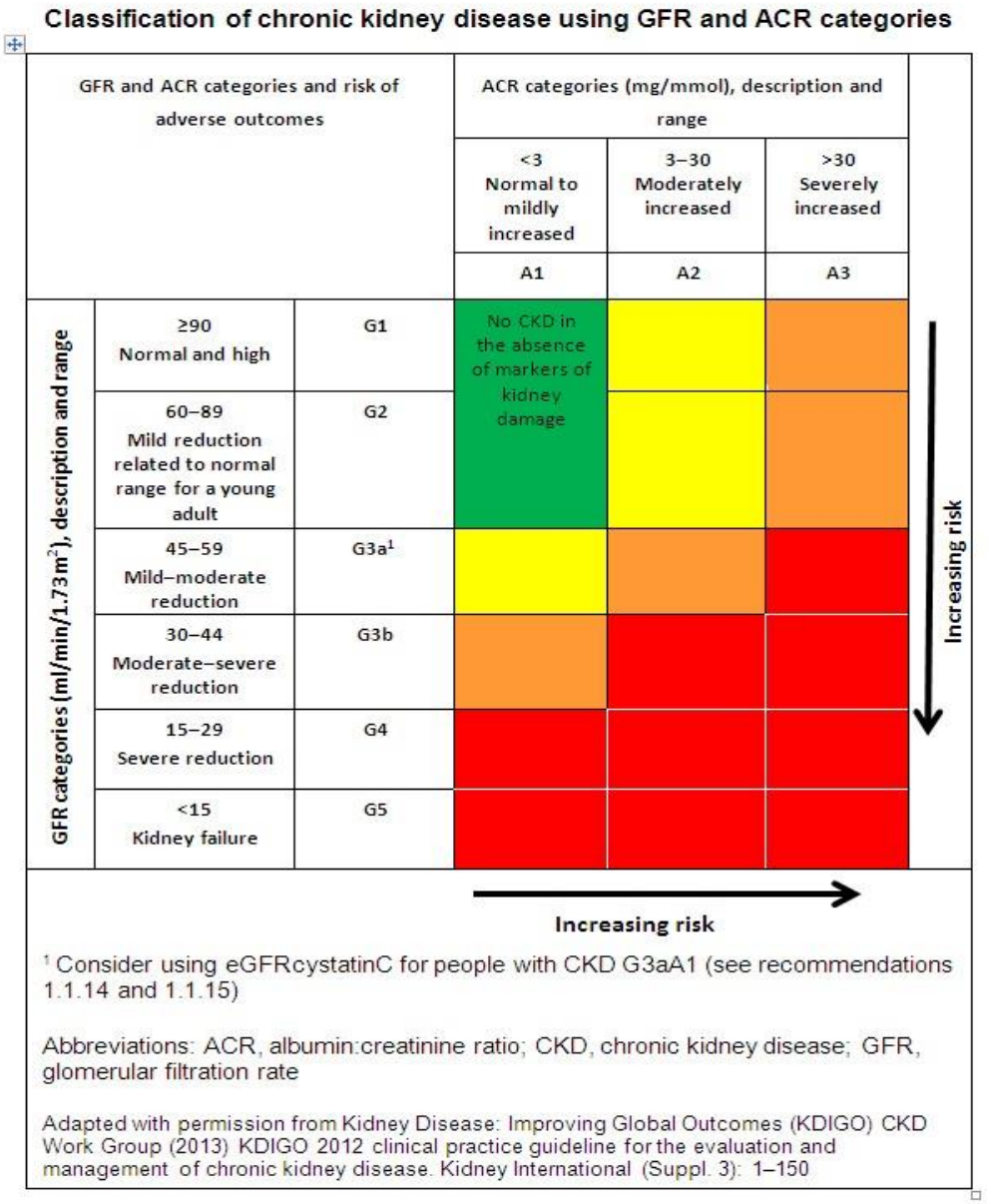


Figure 1-2: The classification of CKD.[6]

1.1.5. Fluid status in CKD

Patients with moderate to particularly advanced stages of chronic kidney disease (CKD) are often affected by fluid overload, which has been linked to pulmonary edema, left ventricular hypertrophy (LVH), hypertension, and congestive heart failure (CHF).[5,6]

Reduced sodium filtration and improper tubular reabsorption suppression brought on by progressive loss of renal function eventually result in volume expansion.[7]

Since it can be challenging to diagnose fluid overload in a clinical setting, diuretics are typically prescribed in response to physical symptoms of edema and high blood pressure. Edema is a useful tool for estimating excess extravascular volume, but it is not very useful for estimating excess intravascular volume. Additionally, it's important to hold onto several litres of water until visible physical signs of edema appear.[8]

Extracellular fluid volume expansion is often caused by renal salt and water retention. An apparent increase in the volume of interstitial fluid, most commonly caused by heart failure, cirrhosis with ascites, and nephrotic syndrome, leads to generalized edema.[9]

1.1.6. Hemodialysis

The hemodialysis system's objectives are to safely transport the patient's blood to the dialyzer, facilitate the effective removal of uremic toxins and extra fluid, and return the cleared blood to the patient. The main components of the dialysis system are the extracorporeal blood circuit, the dialyzer, the dialysis machine, and the water purification system.[3]

Hemodialysis achieves clearance of blood solutes by convection and diffusion against a concentration gradient with dialysate flowing countercurrent to blood separated by a semipermeable dialyzer membrane.[3]

Hemodialysis commonly performed a 3 hours treatment session at an outpatient dialysis unit. Frequent and longer treatments provide better control of volume status and serum electrolyte; some patient performs hemodialysis at home four to five times per week but with shorter treatment session.[3]

The hydrostatic and oncotic pressures in each compartment control the fluid exchange between the plasma and the interstitium, according to the Starling equation. A drop in plasma oncotic pressure or an increase in capillary hydrostatic pressure might lead to interstitial fluid overflow. To put it another way, edema can arise from either a decrease in fluid movement from the interstitial space to the intravascular compartment or an increase in fluid movement from the intravascular compartment to the interstitial space, or from both.[10]

1.1.7 Pulmonary hypertension

Pulmonary hypertension (PH) is a heterogenous disease involving pathogenic remodeling of the pulmonary vasculature, which increases pulmonary artery pressure and vascular resistance. The most common causes of PH are left heart or primary lung disease; PH is also observed in some patients as a late complication of luminal pulmonary embolism. Pulmonary arterial hypertension (PAH) is an uncommon, but distinct, PH subtype characterized by the interplay between molecular and genetic events that cause an obliterative arteriopathy and symptoms of dyspnea, chest pain, and syncope. If left untreated, PH carries a high mortality rate, largely owing to decompensated right heart failure.

There have been significant advances in the field with regard to understanding disease pathogenesis, diagnosis, and classification. For example, the mean pulmonary artery pressure (mPAP) used to diagnose PH has been lowered from ≥25 mmHg to >20 mmHg. This adjustment emphasizes earlier detection of PH, as a substantial delay in diagnosis of up to 2 years is common and has important implications for both quality of life and life span. Clinicians should be able to recognize the signs and symptoms of PH and complete a systematic evaluation in at-risk patients. In this way, prompt diagnosis, appropriate treatment, and optimized patient outcome are achievable.[1]

PATHOBIOLOGY

Apoptosis resistance, cell proliferation, dysregulated metabolism, and increased oxidant stress involving pulmonary vascular cells and adventitial fibroblasts underlie the pathogenesis of PAH. These events lead to hypertrophic, fibrotic, and plexogenic remodeling of distal (small) pulmonary arterioles, which decreases vascular compliance and promotes in situ thrombosis. Abnormalities in multiple molecular pathways and genes that regulate pulmonary vascular endothelial and smooth muscle cells have been identified. These abnormalities include decreased expression of the voltage-regulated potassium channel, mutations in the bone morphogenetic protein receptor-2, increased tissue factor expression, overactivation of the serotonin transporter, hypoxiainduced activation of hypoxia-inducible factor-1α, and activation of nuclear factor of activated T cells. Recently, overlap in the pathobiology of PAH with solid tumor cancers has been recognized, leading to the identification of pyruvate dehydrogenase kinase and neural precursor cell expressed developmentally downregulated 9 (NEDD9) as important in PAH. Thrombin deposition in the pulmonary vasculature that develops as an independent abnormality or as a result of endothelial dysfunction may amplify the obliterative arteriopathy.[1]

Pathophysiology

In PAH, pathologic changes to pulmonary arterial compliance result in a progressive increase in total pulmonary vascular resistance (PVR). The resting PVR

increases through the temporal progression of PAH, corresponding to a rise in mPAP. To preserve cardiac output (CO) in the face of elevated right ventricular afterload, right ventricular work must increase. A sustained (or progressive) increase in right ventricular work causes a shift in the efficiency of right ventricular systolic function by which maintaining pulmonary circulatory pressure depletes myocardial energy. These changes occur at the expense of energy normally reserved to maintain optimal blood perfusion through the alveolar-capillary interface for blood oxygenation, a process termed right ventricularpulmonary arterial uncoupling. In end-stage PAH, the CO declines, leading to a decrease in mPAP (, and extrapulmonary vascular manifestations are frequent; these include overactivation of neurohumoral signaling, renal failure, and volitional muscle atrophy, which is likely due to deconditioning.[1]

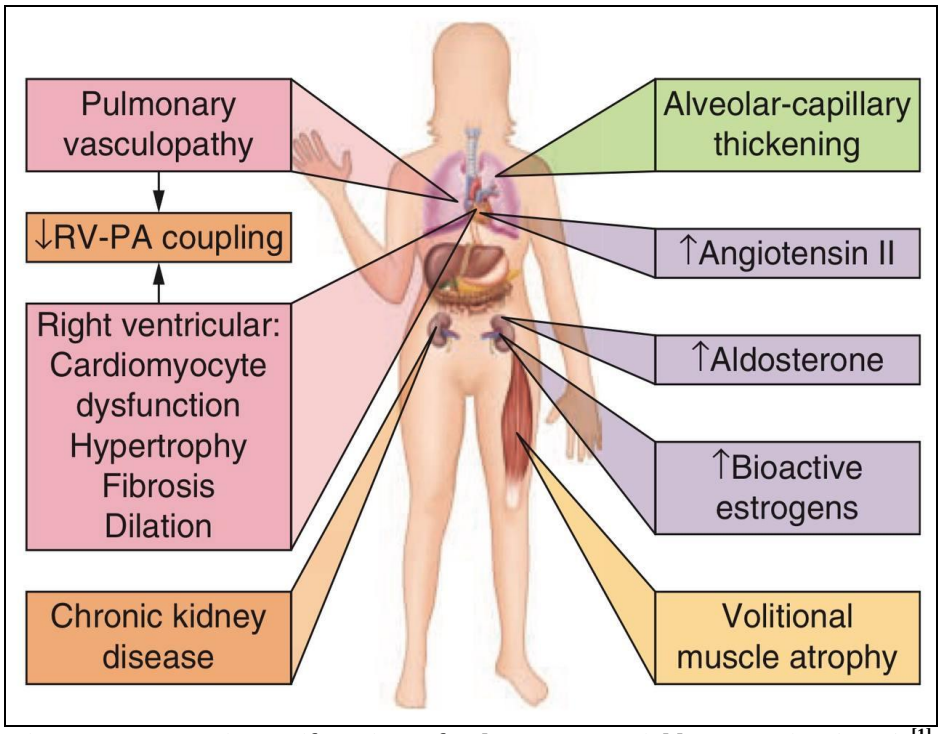


Figure 1-3: Systemic manifestations of pulmonary arterial hypertension (PAH).[1]

DIAGNOSIS

The diagnosis of PH can be missed without a reasonable index of suspicion. Indeed, findings from clinical registries suggest that PH is often overlooked, even among patients with numerous risk factors. This shortcoming may be because PH symptoms are nonspecific, insidious, and overlap considerably with many common conditions, such as asthma or left heart failure. Additionally, there is a misconception that in patients with comorbid cardiopulmonary conditions (e.g., interstitial lung disease, mitral valve disease), PH is merely an extension of the underlying disease rather than a specific clinical entity. Most patients will present with dyspnea and/or fatigue, whereas edema, chest pain, presyncope, and syncope are less common and associated with more advanced disease. In early phases of PAH, the physical examination is often unrevealing. As the disease progresses, there may be evidence of right ventricular failure with elevated jugular venous pressure, lower extremity edema, and ascites. Additionally, the cardiovascular examination may reveal an accentuated P component of the second heart sound, a right-sided S 3 or S4, and a 2 holosystolic tricuspid regurgitant murmur. It is also important to seek signs of the diseases that are commonly concurrent with PH: clubbing may be seen in some chronic lung diseases, sclerodactyly and telangiectasia may signify scleroderma (or the limited cutaneous form, CREST [calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia]), and crackles on examination of the lungs and systemic hypertension may be clues to left-sided systolic or diastolic heart failure.[1]

PH has recently been recognized as a common complication of chronic kidney disease (CKD) and end-stage renal disease (ESRD). To understand this association, it is important to review the hemodynamic determinants of PH and to delineate the spectrum of disorders causing PH. Hemodynamic derangements that result in PH are physiologically characterized by the equation for peripheral vascular resistance (PVR), derived from Ohm's law: resistance=change in pressure divided by flow. Rearranging and simplifying the equation illustrates the pathological conditions that result in elevated PAP (Figure 1-3).[11]

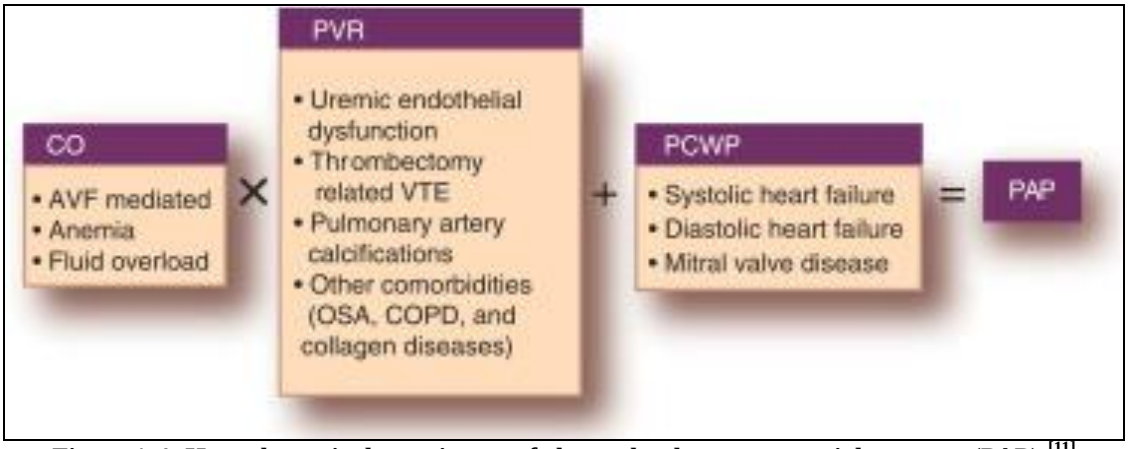


Figure 1-4: Hemodynamic determinants of elevated pulmonary arterial pressure (PAP).[11]

In common clinical practice, PAP is estimated by echocardiography using the modified Bernoulli equation: PAP=4 × (tricuspid systolic jet velocity)2+estimated right atrial pressure, typically measured by vena cava diameter or added based on an assumed, fixed value.8,9 The limitations of echocardiography in firmly diagnosing PH are well established and include inaccuracies in estimating pulmonary pressure when the tricuspid jet is minimal or difficult to visualize and the reliance on indirect or assumed measurements of right atrial pressure.10 Nevertheless, routine reliance on echocardiography to define PH by proxy estimates is driven by a number of factors including cost-effectiveness, the safety of noninvasive measurements, ease of use as a screening tool, and the wider availability of echocardiography compared with right heart catheterization. Despite these advantages, the importance of right heart catheterization in investigating PH in patients with kidney disease cannot be overemphasized. As we will discuss, PH is a multifactorial process in ESRD/CKD, and echocardiography is limited in its ability to define the particular contribution of cardiac output (CO), pulmonary capillary wedge pressure (PCWP), and PVR to the elevated PAP.[11]

Classifications

Table 1-3: WHO Diagnostic Groups of pulmonary hypertension.[12]

WHO group	Examples	Epidemiological overlap with kidney disease
1. PAH	IPAH, heritable IPAH, connective tissue disease, portal hypertension, HIV infection, and drug and toxin–induced PAH	Recurrent episodes of AKI in IPAH patients. Overlap syndromes: HIV, scleroderma, nephrogenic sclerosing dermatopathy, and end-stage liver disease
2.Pulmonary hypertension owing to left heart disease	Systolic dysfunction, diastolic dysfunction, or valvular heart disease	High prevalence of systolic and diastolic heart failure in CKD and ESRD patients
3.Pulmonary hypertension owing to disorders of the lung/respiratory system	COPD, interstitial lung disease, sleep apnea, and obesity hypoventilation	High prevalence of sleep apnea and COPD in CKD and ESRD patients
4.Chronic thromboembolic pulmonary hypertension	Proximal or distal thomboembolic occlusion of the proximal or distal pulmonary vasculature	Increased incidence of VTE in ESRD patients Pulmonary embolism following AV-access thrombectomy
5.Pulmonary hypertension with unclear or multifactorial mechanisms	Myeloproliferative disorders, sarcoidosis, glycogen-storage disease, chronic kidney disease, and miscellaneous disorders	Unexplained PH in CKD/ESRD

Treatment

Treatment of PH depends on the cause, again highlighting the importance of accurate assessment of the etiology of PH in CKD and ESRD patients. In general, targeted PAH therapies are indicated in group 1 PH. For patients with 'secondary' PH, due to left-sided heart disease, pulmonary disease, or CTEPH, treatment is aimed at the underlying process.

Adjunctive therapies for PH include oxygen, diuretics, anticoagulation, and exercise-training therapy. Oxygen is the cornerstone of therapy in patients with group 3 PH,

where there is proven mortality benefit in patients with chronic obstructive pulmonary disease and hypoxia.[13,14] Supplemental oxygen is recommended in patients with any type of PH who are hypoxemic, with a goal of maintaining the oxygen saturation above 90% with activity and rest. Diuretics are used as primary therapy in patients with group 2 PH with CHF,[15] and should be considered in all patients with PH who have edema or hepatic congestion.[16] Patients with PH are at increased risk of pulmonary embolism because of dilated right heart chambers and limitation in physical activity, leading to venous stasis. Anticoagulation is required in group 4, CTEPH, and is also, albeit weakly, recommended in patients with idiopathic PAH (group 1) given retrospective evidence of a modest mortality benefit.[17] Exercise therapy is both safe and efficacious; patients enrolled in an exercise-training program improved both WHO functional class and six-minute walk distance.[18]

Published guidelines recommend PAH-targeted therapy in patients who have class II or worse functional status, defined by shortness of breath, fatigue, or chest pain with ordinary physical activity despite adequate primary therapy. It is important to emphasize that targeted therapies were studied only in patients with group 1 PH (PAH), and there are important limitations to the use of these agents in other forms of PH. In fact, there is evidence that pulmonary vasodilator treatment is unsafe in some types of PH by worsening ventilation/perfusion mismatch in patients with group 3 PH or by increasing left ventricular end-diastolic pressure in patients with group 2 PH.[19-22]

Once the decision has been made to consider initiation of targeted therapy, patients require invasive hemodynamic assessment with right heart catheterization and vasoreactivity testing. Positive vasoreactivity testing may identify a small subgroup of patients who warrant trial of an oral dihydropyridine calcium channel blocker or diltiazem before beginning advanced therapy.[23] Only one study of right heart catheterization has been performed in CKD and ESRD patients, and in this study none of the six patients with pre-capillary PH demonstrated positive vasoreactivity, suggesting that there are few patients with PH and CKD/ESRD in whom this therapy should be initiated.[24]

Currently approved therapies for PAH include agents in three classes: prostanoids, endothelin receptor antagonists (ERAs), and cyclic guanosine monophosphate-specific phosphodiesterase type 5 inhibitors. Each class of drugs has a unique mechanism that addresses specific endothelial abnormalities (Table1-3). Randomized controlled trials have demonstrated the clinical benefit of these agents on several relevant end points, including exercise capacity, functional class, and delay in clinical worsening.

Table 1-3: Pharmacologic treatment of pulmonary hypertension in patients with chronic or end-stage kidney disease.[25-33]

Drug class	Mechanism of action	Drug (brand name): route	Clinical benefit	Renal adjustment
Proteinoids	Vasodilatation of pulmonary and systemic vascular beds; inhibition of platelet aggregation	Epoprostenol (Flolan, Veletri): intravenous Treprostinil (Remodulin): intravenous/subcutaneous Treprostinil (Tyvaso): inhaled Iloprost (Ventavis): inhaled Iloprost (Ilomedin): intravenous[c]	Improved quality of life and exercise capacity Decreased PAP Trend toward decreased mortality	Epoprostenol/Treprostinil: no dose adjustment in patients with renal dysfunction Iloprost: reduce starting dose by 50% in patients undergoing HD
Endothelin receptor antagonists	Inhibition of vasoconstriction and proliferation of vascular smooth muscle cells	Bosentan (Tracleer): oral Ambrisentan (Letaris): oral	Improved exercise capacity Reduced shortness of breath Decreased PAP and PVR and increased CO	No dose adjustment in advanced CKD or in patients undergoing HD
PDE5 inhibitors	Enhancement of the vasodilator effect of NO	Sildenafil (Revatio): oral/intravenous Tadalafil (Adcirca): oral	Improved exercise capacity and pulmonary hemodynamics	Sildenafil: No dose adjustment in patients with renal dysfunction Tadalafil: Cr clearance 31–80, reduce starting dose by 50%. Contraindicated in Cr Clearance <30 or HD

Fig. 2-1: AK98 Dialysis machine.

The BCM - Body Composition Monitor was specifically designed to determine the amount of fluid overload that arises in patients suffering from renal failure. This allows for a simple, non-invasive and objective assessment of an individual patient's fluid status.

As a result, the BCM - Body Composition Monitor may help the clinician to determine a patient's individual dry weight more accurately and, as a result, to remove the correct amount of fluid.

Advantages of bioimpedance-guided Fluid Management

The BCM - Body Composition Monitor allows for the practical and accurate determination of the fluid status in contrast to alternative assessment methods.

Assessing the fluid status with the BCM - Body Composition Monitor:

- Is non-invasive, simple and fast (approx. 10 sec. for pure measuring process)
- Is highly reproducible.
- Validated against standard reference methods.
- Is possible with HD, PD and pediatric patients.
- Can be used for a more accurate dialysis dose assessment by providing the urea distribution volume as an input on the Online Clearance Monitor of most HD devices from Fresenius Medical Care.
- The BCM - Body Composition Monitor provides a quantitative measure of lean tissue and fat tissue mass because it is able to distinguish muscle mass from fluid overload. This allows for an improved diagnosis of malnutrition in ESRD patients and allows for an adequate therapy intervention.[54]

Figer 2-2: Body Composition Monitor.

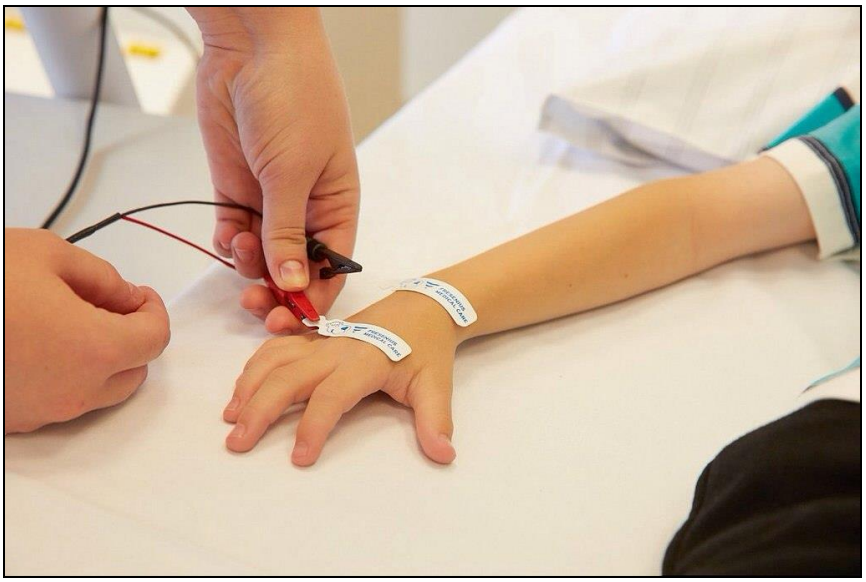


Figure 2-3: Showing how BCM data collected.

2.6. Ethical consideration and official approval.

The information was anonymous. Consent was verbal, names were removed and replaced by identification codes. All information was kept confidential in a password secured laptop and data is used exclusively for the research purposes. The administrative approval was granted from the Council of Iraqi board of Medical Specialization.

2.7. Statistical analysis

The collected data were coded, entered, presented, and analyzed by computer using the available data base software program statistical package of IBM SPSS-29 (IBM Statistical Packages for Social Sciences- version 29, Chicago, IL, USA). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means or ANOVA test for difference among more than two independent means. The significance of difference of different percentages (qualitative data) were tested using Pearson Chi-square test (r 2-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05.[55-58]

Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. The correlation coefficient value (r) either positive (direct correlation) or negative (inverse correlation) with value <0.3 represent no correlation, 0.3-<0.5 represent weak correlation, 0.5-<0.7 moderate strength, >0.7 strong correlation. In addition to correlation the r2 was calculated (The coefficient of determination), i.e. when value of r=0.58, then r2=0.34, this means that 34% of the variation in the values of y may be accounted for by knowing values of x or vice versa.[55-58]

Receiver Operating Characteristic "ROC" curve technique was used in order to determine the use of any parameter as diagnostic or screening tool for disease and the ability to determine the "cut-off value" which of optimum sensitivity and specificity for diagnosing disease. The ROCS area "Area Under the Curve "AUC" explanation as follows,

- 0.9---- "Perfect"
- 0.8--- "Good"
- 0.7--- "Fair"
- 0.6--- "Poor"
- <0.6 "Failure"

The sensitivity, specificity, false negative%, false positive%, predictive value of positive test, predictive value of negative test, and accuracy rate were calculated according to the following equations

- Test Disease Healthy Totals
- Positive True Positive False Positive Total Positives
- Negative False Negative True Negative Total Negatives
- Total Total Disease Total Healthy Grand total
- Sensitivity= (True Positive/Total Disease) x 100
- Specificity= (True Negative/Total Healthy) x 100
- False Negative%= (False Negative/Total Disease) x 100
- False Positive%= (False Positive/Total Healthy) x 100
- Predictive value of Positive test= (True Positive/Total Positives) x 100
- Predictive value of Negative test = (True Negative/Total Negatives) x 100
- Accuracy rate= [(True Positive+True Negative)/(Total Disease+Total Healthy)]x100

Sample size

All eligible patients filled out the consent form and completed the research tool in a written format. The sample size was calculated using the following formula:

Where n is the sample size, α is the first type, Z is the table-based normal distribution index that is considered at 5% type-one error (P<0.05), σ represents the small variable variance, and d shows the accuracy of quantitative variable estimation. In this study, a first type error, z, σ, and d equal to 0.05, 96.3, 7.38, and 0.99, respectively. After adjusting for the non-response of 10%, 86 were considered as the sample size, and 100 were included in the data analysis.[59]

A sample size was calculated using a design effect of 2, 80% statistical power with a 2-sided test, and α = 0.05 to detect a decrease of 10%, where 30% was assumed to be the percentage of persons estimated to have an irregular legal status at time 1 (this study) and 20% was assumed to be the percentage at time 2 (the next round of this study).[60]

RESULTS

Table (3-1) showing demographic distribution

Demographic Data		**No.**	**%**
Age (years)	Mean±SD (Range)	49.0±12.5	(20-69)
Sex	Male	73	73.0
Mode of hemodialysis	Hemodialysis	66	66.0
	Hemodiafiltration	34	34.0
Duration on hemodialysis (years)	Less than one year	19	19.0
	More than one year	81	81.0
Number of session per week	AVF	88	88.0
	PERMI CATH	12	12.0
Time per session (hours)	3.0	8	8.0
	3.5	30	30.0
	4.0	62	62.0
Type of access	AVF	88	88.0
	PERMI CATH	12	12.0
Daily UOP	oliguria	66	66
	500-1000 cc	25	25
	More than 1000cc	9	9
Use diuretic	Yes	48	48.0
	No	52	52.0
Diet & fluid restriction	Yes	23	23.0
	No	77	77.0
Ultrafiltration (UF) per session	2.5L---	4	4.0
	3.0L---	33	33.0
	3.5L---	30	30.0
	4.0L---	33	33.0

Viral screen	Positive	22	22.0
	Negative	78	78.0
Total serum protein (g/dL)		6.94±0.78	(5.0-9.0)
Serum albumin (g/dL)		4.01±0.37	(3.1-4.6)

Table 3-2: Showing the causes of ESKD.

Cause of ESKD	No.	%
Unknown	15	15
Diabetes mellitus	33	33
Hypertension	25	25
Nephrotic syndrome	11	11
SLE	7	7
Interstitial nephritis	3	3
ADPKD	4	4
Reflex Nephropathy	2	2
Family history	18	18.0

Table 3-3: Showing the risk factors.

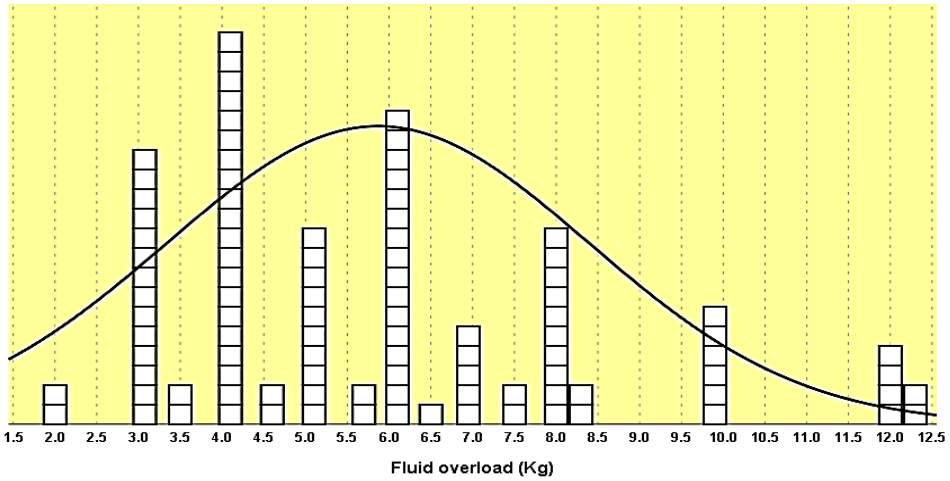
Risk factors		No.	%
Smoking		25	25.0
Hypertension		91	91.0
Diabetes mellitus		63	63.0
IHD		34	34.0
NSAID abuse		5	5.0
SLE		4	4.0
ADPKD		4	4.0
Reflux Nephropathy/ Chronic Interstitial Nephritis		2	2.0
Alport syndrome		2	2.0
Nephrotic syndrome		3	3.0
Family history		18	18.0
Family history	Brother	7	
	Father (ADPKD)	4	
	Mother	5	
	Uncle	2	

Table 3-4: Showing the clinical features.

Clinical features	No.	%
Uncontrolled hypertension	71	71.0
Orthopnea	77	77.0
Leg edema	94	94.0
Pulmonary odema	94	94.0
Raised JVP	36	36.0
Ascites	16	16.0
Pleural effusion	77	77.0

Table 3-5: Showing the BCM findings.

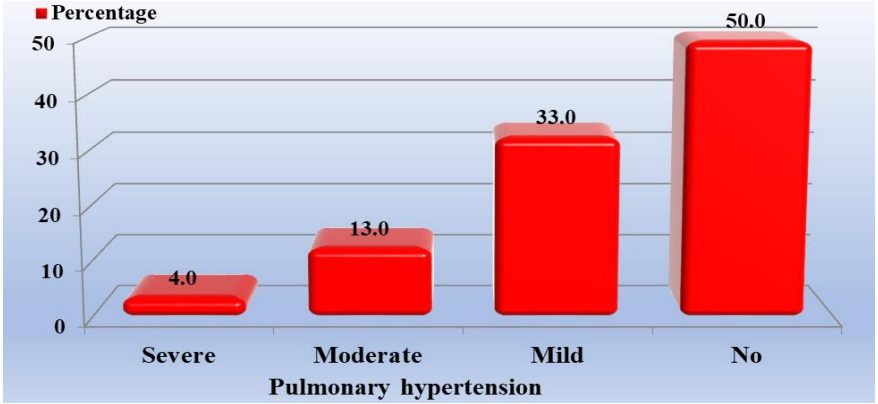
BCM		No.	%
Dry weight (Kg)		77.05±18.57	(45-134)
Actual weight (Kg)		84.82±19.05	(49-143)
Fluid overload (Kg)	<5Kg	40	40.0
	5---9	50	50.0
	=>10Kg	10	10.0
Overhydration (Kg)		5.87±2.53	(2.0-12.3)



Figer 3-1: showing the fluid overload.

Table 3-6: Showing the Echo findings.

Echo findings		No.	%
Pulmonary hypertension	Yes	50	50.0
LVH	Yes	97	97
Pericardial tamponade	Yes	2	2
Ejection fraction (EF%)	EF <50%	36	36.0
	EF =>50%	64	64.0
	Mean±SD (Range)	51.79±9.67	(31-65)
Treatment for pulmonary hypertension (n=50)	Yes	6	12.0



Figer 3-2: Showing the pulmonary hypertension.

Table 3-7: p value Associations of Demographic Data with Pulmonary Hypertension.

Demographic Data		Pul. Hypertension		No		P value
		No.	%	No.	%	
Age (years)	<30years	5	10.0	6	12.0	0.172
	30---39	7	14.0	3	6.0	
	40---49	19	38.0	11	22.0	
	50---59	11	22.0	16	32.0	
	=>60years	8	16.0	14	28.0	
	Mean±SD	47.3±11.9		50.7±13.0		0.175
Sex	Male	30	60.0	43	86.0	0.003*
	Female	20	40.0	7	14.0	
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.						
#Significant difference between two independent means using Students-t-test at 0.05 level.						

Hemodialysis		Pul. Hypertension		No		P value
		No.	%	No.	%	
Mode of hemodialysis	HD	35	70.0	31	62.0	0.398
	HDF	15	30.0	19	38.0	
Duration on hemodialysis (years)	Less than one	9	18.0	10	20.0	0.691
	One	3	6.0	8	16.0	
	Two	7	14.0	9	18.0	
	Three	12	24.0	7	14.0	
	Four	4	8.0	3	6.0	
	Five	4	8.0	5	10.0	
	Six	2	4.0	2	4.0	
	Seven & more	9	18.0	6	12.0	
	Mean±SD	4.0±3.4		3.0±2.2		0.081
Type of access	AVF	40	80.0	48	96.0	0.014*
	PERMI CATH	10	20.0	2	4.0	
Number of session per week	2	29	58.0	23	46.0	0.230
	3	21	42.0	27	54.0	
Time per session (hours)	3.0	-	-	8	16.0	
	3.5	17	34.0	13	26.0	
	4.0	33	66.0	29	58.0	
Daily UOP	Nil	12	24.0	3	6.0	0.084
	Few cc	23	46.0	28	56.0	
	100 cc	3	6.0	1	2.0	
	200 cc	4	8.0	4	8.0	
	300 cc	3	6.0	6	12.0	
	500 cc	1	2.0	3	6.0	
	One Liter	4	8.0	2	4.0	
	Two Liters	-	-	3	6.0	
Daily UOP	Nil	12	24.0	3	6.0	0.042*
	Few cc	23	46.0	28	56.0	
	100-500cc	11	22.0	14	28.0	
	One Liter	4	8.0	2	4.0	
	Two Liters	-	-	3	6.0	
Use diuretic	Yes	20	40.0	28	56.0	0.109
	No	30	60.0	22	44.0	
Diet & fluid restriction	Yes	10	20.0	13	26.0	0.476
	No	40	80.0	37	74.0	
Ultra filtration (UF) per session	2.5L---	-	-	4	8.0	0.154
	3.0L---	16	32.0	17	34.0	
	3.5L---	18	36.0	12	24.0	
	4.0L---	16	32.0	17	34.0	
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.						
#Significant difference between two independent means using Students-t-test at 0.05 level.						

Table 3-8: p value Associations of Risk factors with Pulmonary Hypertension.

Risk factors		Pul. Hypertension		No		P value
		No.	%	No.	%	
Smoking	Yes	7	14.0	18	36.0	0.011*
	No	43	86.0	32	64.0	
Hypertension	Yes	47	94.0	44	88.0	0.295
	No	3	6.0	6	12.0	
Diabetes mellitus	Yes	29	58.0	34	68.0	0.300
	No	21	42.0	16	32.0	
IHD	Yes	16	32.0	18	36.0	0.673
	No	34	68.0	32	64.0	
NSAID abuse	Yes	3	6.0	2	4.0	0.646
	No	47	94.0	48	96.0	
SLE	Yes	-	-	4	8.0	0.041*

	No	50	100.0	46	92.0	
ADPKD	Yes	1	2.0	3	6.0	0.307
	No	49	98.0	47	94.0	
Reflux Nephropathy/ Ch. Interstitial Nephritis	Yes	1	2.0	1	2.0	-
	No	49	98.0	49	98.0	
Alport syndrome	Yes	2	4.0	-	-	0.153
	No	48	96.0	50	100.0	
Nephrotic syndrome	Yes	1	2.0	2	4.0	0.558
	No	49	98.0	48	96.0	
Family history	Yes	9	18.0	9	18.0	-
	No	41	82.0	41	82.0	
Family history.	Father (ADPKD)	1	11.1	3	33.3	0.214
	Mother	3	33.3	2	22.2	
	Brother	5	55.6	2	22.2	
	Uncle	-	-	2	22.2	
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.						

Table 3-9: p value Associations of Clinical features with Pulmonary Hypertension.

Clinical features		Pul. Hypertension		No		P value
		No.	%	No.	%	
Uncontrolled hypertension	Yes	36	72.0	35	70.0	0.826
	No	14	28.0	15	30.0	
Orthopnea	Yes	40	80.0	37	74.0	0.476
	No	10	20.0	13	26.0	
Leg edema	Yes	48	96.0	46	92.0	0.400
	No	2	4.0	4	8.0	
Pulmonary odema	Yes	48	96.0	46	92.0	0.400
	No	2	4.0	4	8.0	
Raised JVP	Yes	19	38.0	17	34.0	0.677
	No	31	62.0	33	66.0	
Ascitis	Yes	9	18.0	7	14.0	0.585
	No	41	82.0	43	86.0	
Pleural effusion	Yes	38	76.0	39	78.0	0.812
	No	12	24.0	11	22.0	
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.						

Table 3-10: p value Associations of Lab and BCM with Pulmonary Hypertension.

Lab and BCM		Pul. Hypertension		No		P value
		No.	%	No.	%	
Viral screen	Positive	11	22.0	11	22.0	-
	Negative	39	78.0	39	78.0	
Total serum protein (g/dl)		7.06±0.80		6.83±0.76		0.135
Serum albumin (g/dl)		4.03±0.36		3.99±0.38		0.573
Dry weight (Kg)		76.01±16.96		78.09±20.18		0.577
Actual weight (Kg)		84.57±17.26		85.06±20.86		0.898
Overhydration (Kg)	<5Kg	17	34.0	23	46.0	0.275
	5---9	26	52.0	24	48.0	
	=>10Kg	7	14.0	3	6.0	
	Mean±SD	6.24±2.45		5.49±2.58		0.140
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.						
#Significant difference between two independent means using Students-t-test at 0.05 level.						

Table 3-11: p value Associations of Echo findings with Pulmonary Hypertension.

Echo findings		Pul. Hypertension		No		P value
		No.	%	No.	%	
Pulmonary hypertension	Yes	50	100.0	-	-	
	No	-	-	50	100.0	
Pulmonary hypertension	Severe	4	8.0	-	-	

(n=50)	Moderate	13	26.0	-	-	
	Mild	33	66.0	-	-	
LVH	Severe	-	-	-	-	0.023*
	Moderate	18	36.0	8	16.0	
	Mild	32	64.0	39	78.0	
	No	-	-	3	6.0	
Pericardial tamponade	Severe	-	-	-	-	0.153
	Moderate	-	-	-	-	
	Mild	2	4.0	-	-	
	No	48	96.0	50	100.0	
Ejection fraction (EF%)	EF <50%	21	42.0	15	30.0	0.211
	EF =>50%	29	58.0	35	70.0	
	Mean±SD	49.34±9.76		54.24±9.03		0.011#
Treatment for pulmonary hypertension (n=50)	Yes	6	12.0	-	-	
	No	44	88.0	-	-	
*Significant difference between percentages using Pearson Chi-square test (χ^2-test) at 0.05 level.						
#Significant difference between two independent means using Students-t-test at 0.05 level.						

Relation with fluid overload (Kg)

Table 3-12: p value Associations of Demographic Data with Fluid overload.

Demographic Data		**Fluid overload (Kg)**		**P value**
		No.	**Mean±SD**	
Age (years)	<30years	11	6.72±3.08	0.609
	30---39	10	6.22±2.72	
	40---49	30	6.06±2.49	
	50---59	27	5.47±2.62	
	=>60years	22	5.50±2.14	
Sex	Male	73	5.72±2.54	0.361
	Female	27	6.25±2.50	
#Significant difference between two independent means using Students-t-test at 0.05 level.				
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.				

Hemodialysis		**Fluid overload (Kg)**		**P value**
		No.	**Mean±SD**	
Mode of hemodialysis	HD	66	5.99±2.47	0.497
	HDF	34	5.63±2.66	
Duration on hemodialysis (years)	Less than one	19	5.46±1.77	0.410
	One	11	6.06±2.47	
	Two	16	5.99±2.89	
	Three	19	6.96±3.01	
	Four	7	6.44±2.60	
	Five	9	5.22±2.82	
	Six	4	5.63±2.21	
	Seven & more	15	4.91±2.13	
Type of access	AVF	88	5.95±2.61	0.359
	PERMI CATH	12	5.23±1.76	
Number of session per week	2	52	6.09±2.64	0.355
	3	48	5.62±2.41	
Time per session (hours)	3.0	8	6.29±2.79	0.696
	3.5	30	6.10±2.39	
	4.0	62	5.70±2.59	
Daily UOP	Nil	15	5.25±2.14	0.166
	Few cc	51	5.99±2.46	
	100 cc	4	6.30±3.26	
	200 cc	8	4.21±0.80	
	300 cc	9	5.96±3.41	
	500 cc	4	4.90±1.43	
	One Liter	6	7.72±1.44	

	Two Liters	3	7.93±5.25	
Daily UOP	Nil	15	5.25±2.14	0.108
	Few cc	51	5.99±2.46	
	100-500cc	25	5.29±2.53	
	One Liter	6	7.72±1.44	
	Two Liters	3	7.93±5.25	
Use diuretic	Yes	48	6.18±2.61	0.229
	No	52	5.57±2.45	
Diet & fluid restriction	Yes	23	5.57±2.95	0.531
	No	77	5.95±2.41	
Ultra filtration (UF) per session	2.5L---	4	4.36±2.63	0.003^
	3.0L---	33	5.28±1.76	
	3.5L---	30	5.30±2.24	
	4.0L---	33	7.14±2.99	
#Significant difference between two independent means using Students-t-test at 0.05 level.				
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.				

Table 3-13: p value Associations of Risk factors with fluid overload.

Risk factors		**Fluid overload (Kg)**		**P value**
		No.	**Mean±SD**	
Smoking	Yes	25	6.03±2.76	0.707
	No	75	5.81±2.47	
Hypertension	Yes	91	5.93±2.57	0.443
	No	9	5.24±2.16	
Diabetes mellitus	Yes	63	5.80±2.56	0.742
	No	37	5.98±2.51	
IHD	Yes	34	5.87±2.26	0.990
	No	66	5.86±2.68	
NSAID abuse	Yes	5	4.86±1.92	0.365
	No	95	5.92±2.56	
SLE	Yes	4	7.32±3.35	0.241
	No	96	5.81±2.50	
ADPKD	Yes	4	5.63±2.21	0.847
	No	96	5.88±2.55	
Reflux Nephropathy/ Chronic Interstitial Nephritis	Yes	2	8.15±0.21	0.199
	No	98	5.82±2.54	
Alport syndrome	Yes	2	5.50±3.54	0.838
	No	98	5.87±2.53	
Nephrotic syndrome	Yes	3	4.93±4.24	0.520
	No	97	5.89±2.49	
Family history	Yes	18	6.28±3.12	0.449
	No	82	5.78±2.40	
Family history.	Father (ADPKD)	4	5.63±2.21	0.078
	Mother	5	8.26±3.73	
	Brother	7	4.41±1.48	
	Uncle	2	9.15±4.45	
#Significant difference between two independent means using Students-t-test at 0.05 level.				
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.				

Table 3-14: p value Associations of clinical features with fluid overload.

Clinical features		Fluid overload (Kg)		P value
		No.	Mean±SD	
Uncontrolled hypertension	Yes	71	6.10±2.64	0.155
	No	29	5.30±2.19	
Orthopnea	Yes	77	6.12±2.58	0.070
	No	23	5.03±2.22	
Leg edema	Yes	94	5.85±2.45	0.791
	No	6	6.13±3.93	
Pulmonary odema	Yes	94	5.94±2.56	0.257
	No	6	4.72±1.93	
Raised JVP	Yes	36	6.57±2.63	0.036#
	No	64	5.47±2.41	
Ascitis	Yes	16	6.38±2.42	0.383
	No	84	5.77±2.55	
Pleural effusion	Yes	77	6.18±2.66	0.021#
	No	23	4.81±1.68	
Viral screen	Positive	22	5.76±2.79	0.824
	Negative	78	5.90±2.47	
#Significant difference between two independent means using Students-t-test at 0.05 level.				
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.				

Table 3-15: p value Associations of echo findings with fluid overload.

Echo findings		Fluid overload (Kg)		P value
		No.	Mean±SD	
Pulmonary hypertension	Yes	50	6.24±2.45	0.140
	No	50	5.49±2.58	
Pulmonary hypertension (n=50)	Severe	4	8.07±1.35	0.148
	Moderate	13	5.40±1.55	
	Mild	33	6.35±2.73	
LVH	Severe	-	-	0.052
	Moderate	26	6.37±2.34	
	Mild	71	5.82±2.56	
	No	3	2.67±.58	
Pericardial tamponade	Severe	-	-	0.230
	Moderate	-	-	
	Mild	2	8.00±2.83	
	No	98	5.82±2.52	
Ejection fraction (EF%)	EF <50%	36	5.78±2.77	0.802
	EF =>50%	64	5.91±2.41	
Treatment for pulmonary hypertension (n=50)	Yes	6	4.95±2.17	0.172
	No	44	6.42±2.46	
#Significant difference between two independent means using Students-t-test at 0.05 level.				
^Significant difference among more than two independent means using ANOVA-test at 0.05 level.				

Table 3-16: Correlations between fluid overload & pulmonary hypertension.

		Fluid overload (Kg)	
		Pul. hypertension	No
Age (years)	r	-0.284*	0.007
	P	0.046	0.960
Duration on hemodialysis (years)	r	-0.167	-0.132
	P	0.245	0.362
Total serum protein (g/dl)	r	0.033	-0.177
	P	0.820	0.218

Serum albumin (g/dl)	r	0.262	-0.208
	P	0.066	0.148
Dry weight (Kg)	r	-0.018	0.213
	P	0.901	0.138
Actual weight (Kg)	r	0.111	0.324*
	P	0.442	0.022
Ejection fraction (EF%)	r	-0.134	0.184
	P	0.352	0.202
*Correlation is significant at the 0.05 level. **Correlation is highly significant at the 0.01 level			

DISCUSSION

In patients with ESKD, all systems of the body may be affected. Therefore, these patients suffered from serious respiratory, cardiovascular and metabolic complications.

The mean of age (years) of the patients in the study was 49.0 ± 12.5, while in the study of Yilmaz et. al.[61] the mean of age was 51.37 ± 15.95. Yoo HH et. al.[62] shows that the mean of age was 60 ± 14.3, while in Ying et. al. the mean of age was 55.0 ± 6.1.[63]

The predominant group among the patients in this study were males (73%), which may indicate higher prevalence of CKD among men or those who lack treatment for their chronic diseases, because of financial, social, and cultural barriers. Same results was exactly found in a study done by Yoo HH et.al.[62], who found the number of males were more than the number of females in his study (54% males). Similar results were found in the study of Ying et. al.[63] where the number of males were 55.3%. In contrast to the study of Yilmaz et. al. the males were 51.9%.[61]

Diabetes mellitus was the most common cause of renal failure.[1] In this study, the major cause of ESKD was DM (33%) of patients, the second cause was hypertension being (25%), similar results were found in the study of Ying et. al.[63] where diabetes mellitus was the major cause of ESKD (37.58%) and (14.04%) respectively. While in the study of Yoo HH et. al.[62] the DM patients were 59.3%, in contrast to the study of Yilmaz et. al.[61] the hypertension was the predominant cause with 36.3%, while the diabetes was 16.8%.

The Duration on hemodialysis (in months) in this study was 42 ± 34.8, similar to Ying et. al.[63] which was 36.80 ± 16.37 in contrast to Yilmaz et. al.[61] was 60.51 ± 17.67.

The type of access of hemodialysis in this study by AVF was 88% and by PERMI CATH was 12%. Similar to the study of Yilmaz et. al.[61] were 79.2% and 20.8% respectively, in contrast to Yoo HH et. al.[62] were 23% and 77%.

The smokers in this study were 25%, similar to that of Yilmaz et. al.[61] in which they were 24%, in contrast to Zhang et. al.[64] in which they were 18.7% and Hsieh CW et. al. were 14.6%.[65]

The mean of serum albumin level in this study was 4.01 ± 0.37, while in Yilmaz et.al.[61], Yoo HH et.al.[62] and Ying et.al.[63] was 3.33 ± 0.35, 3.75 ± 0.4 and 4.01 ± 1.05, respectively.

The mean of overhydration in this study was 5.87 ± 2.53, while in Yilmaz et. al.[61] was 2.06 ± 5.8.

Pulmonary hypertension patients in this study were 50 patients (50%), similar to Yilmaz et.al.[61] in which they were 53.2%, in contrast to Yoo HH et. al.[62] were 19%.

Left ventricular hypertrophy was 97% of patients in this study according to Echo findings, while the Zhang et. al. was 57%.[64]

The mean of Ejection fraction (EF%) in this study was 51.79 ± 9.67, while in Yoo HH et. al.[62] was 74.5 ± 9.35, similar to Ying et. al.[63] which was 55.68 ± 2.02.

During this study, 52% of patients had two sessions of hemodialysis per week, and 38% of the patients spent 3 to 3.5 hours per session; this can lead to an increase in the percentage of them suffering from fluid overload and increase the risk of orthopnea, leg edema, pulmonary edema, raised JVP, ascites and pleural effusion.

Multiple risk factors can lead to renal failure and its complications. The main of them are hypertension and diabetes mellitus. They can lead to an increase in the atherosclerosis of the blood vessels and proteinurea, then deterioration of renal function and developing renal failure, due to poor control of treatment of them.

The main physical signs during examination of patient in this study were uncontrolled hypertension (71%), orthopnea (77%) and leg edema (94%).

One of the factors that increase the prediction of pulmonary hypertension is the residual kidney function which increase the fluid compartment of patient, so in this study 50% of them had pulmonary hypertension; 66% of the patients were oliguric.

Limitation of the study

Small sample size, single center study and short duration of follow-up and the need to evaluate the long-term were the limitation points of the study.

CONCLUSION AND RECOMMENDATION

The conclusion of this study is that there is a direct effect of fluid overload in patients with end-stage kidney disease, which lead to many clinical manifestations, so we recommend fluid restriction, avoid nephrotoxic drugs, good control of the risk factors, adherence to the sessions of hemodialysis with regular follow-up and assessment.

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