"A COMPARATIVE STUDY OF PULMONARY HYPERTENSION AMONG CHRONIC KIDNEY DISEASE (CKD) PATIENTS ON DIALYSIS AND ON CONSERVATIVE LINE OF TREATMENT"

By

Dr. INBA PRAVEEN I

Dissertation Submitted To

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA

In Partial Fulfillment Of The Requirement For The Degree Of

DOCTOR OF MEDICINE
IN
GENERAL MEDICINE

Under The Guidance Of

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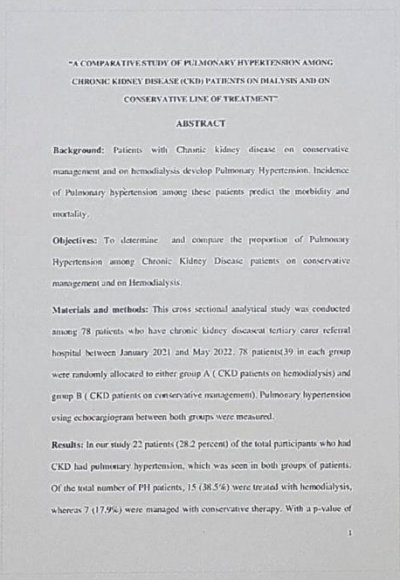

"A COMPARATIVE STUDY OF PULMONARY HYPERTENSION AMONG CHRONIC KIDNEY DISEASE (CKD) PATIENTS ON DIALYSIS AND ON CONSERVATIVE LINE OF TREATMENT"

ABSTRACT

Background: Patients with Chronic kidney disease on conservative management and on hemodialysis develop Pulmonary Hypertension. Incidence of Pulmonary hypertension among these patients predict the morbidity and mortality.

Objectives: To determine and compare the proportion of Pulmonary Hypertension among Chronic Kidney Disease patients on conservative management and on Hemodialysis.

Materials and methods: This cross sectional analytical study was conducted among 78 patients who have chronic kidney diseaseat tertiary carer referral hospital between January 2021 and May 2022. 78 patients(39 in each group were randomly allocated to either group A (CKD patients on hemodialysis) and group B (CKD patients on conservative management). Pulmonary hypertention using echocargiogram between both groups were measured.

Results: In our study 22 patients (28.2 percent) of the total participants who had CKD had pulmonary hypertension, which was seen in both groups of patients. Of the total number of PH patients, 15 (38.5%) were treated with hemodialysis, whereas 7 (17.9%) were managed with conservative therapy. With a p-value of

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LIST OF ABBREVIATIONS

S.NO	ABBREVIATIONS	FULL FORMS
1	PH	Pulmonary Hypertension
2	CKD	Chronic Kidney Disease
3	ECG	Electrocardiogram
4	HD	Hemodialysis
5	mPAP	Mean Pulmonary Artery Pressure
6	ESKD	End Stage Kidney Disease
7	ECHO	Echocardiogram
8	RAP	Right Atrial Pressure
9	PCWP	Pulmonary Capillary Wedge Pressure
10	PVR	Peripheral Vascular Resistance
11	CO	Cardiac Output
12	PPH	Primary Pulmonary Hypertension
13	PVOD	Pulmonary Veno-Occlusive Disease
14	PCH	Pulmonary Capillary Hemangiomatosis
15	PAH	Pulmonary Arterial Hypertension
16	CTD	Connective Tissue Disorder
17	SLE	Sysytemic Lupus Erythmatosus
18	MCTD	Mixed Connective Tissue Disorder

19	IPAH	Idiopathic and hereditary Pulmonary Arterial Hypertension
20	D-PAH	Drug and toxin induced Pulmonary Arterial Hypertension
21	CHD	Congenital Heart Disease
22	VSD	Ventricular Septal Disease
23	HF	Heart Failure
24	HFrEF	Heart Failure with reduced Ejection Fraction
25	HFpEF	Heart Failure with preserved Ejection Fraction
26	RHC	Right Heart Catheterisation
27	WHO	World Health Organisation
28	COPD	Chronic Obstructive Pulmonary Disease
29	ILD	Interstitial Lung Disease
30	OSA	Obstructive Sleep Apnea
31	CTEPH	Chronic Thromboembolic Pulmonary Hypertension
32	CPAP	Continuous Positive Airway Pressure
33	HAPE	High Altitude Pulmonary Edema
34	PLCH	Pulmonary Langerhans Cell Histiocytosis
35	LAM	Lymphangioleiomyomatosis
36	GSD	Glycogen Storage Disorder
37	GD	Gaucher Disease

38	IpcPH	Isolated Post Capillary Pulmonary Hypertension
39	CpcPH	Combined Post Capillary Pulmonary Hypertension
40	LVH	Left Ventricular Failure
41	RV	Right Ventricle
42	LV	Left Ventricle
43	TRV	Tricuspid Regurgitant jet Velocity
44	RVH	Right Ventricular Hypertrophy
45	DPG	Diastolic Pulmonary Gradiant

ABSTRACT

INTRODUCTION:

Patients with Chronic kidney disease on conservative management and on hemodialysis develop Pulmonary Hypertension. Incidence of Pulmonary hypertension among these patients predict the morbidity and mortality.

AIMS AND OBJECTIVES:

To determine and compare the proportion of Pulmonary Hypertension among Chronic Kidney Disease patients on conservative management and on Hemodialysis.

MATERIALS AND METHODS:

This cross sectional analytical study was conducted among 78 patients who have chronic kidney diseaseat tertiary carer referral hospital between January 2021 and May 2022. 78 patients(39 in each group were randomly allocated to either group A (CKD patients on hemodialysis) and group B (CKD patients on conservative management). Pulmonary hypertension using echocargiogram between both groups were measured.

RESULTS:

The current study was conducted among 78 patients with a high prevalence of CKD in the age group between 51-60 years of age (46.2%) and male predominance (56.4%). Diabetes mellitus was reported to be the most common etiology (24.4%), followed by diabetes and hypertension together (24.4%), and CKD of unknown etiology (21.8%).In our study 22 patients (28.2 percent) of the total participants who had CKD had pulmonary hypertension,

which was seen in both groups of patients. Of the total number of PH patients, 15 (38.5%) were treated with hemodialysis, whereas 7 (17.9%) were managed with conservative therapy. With a p-value of 0.044, the current study has a significant difference between the groups receiving hemodialysis and those receiving conservative care, with the hemodialysis group having a greater prevalence of PH (38.5%). A positive correlation was reported between the serum urea, serum creatinine, serum calcium, and alkaline phosphatase which can be associated with the development of PH in CKD patients.

CONCLUSION:

The study showed that both CKD patients receiving dialysis and on conservative management had a significant incidence of pulmonary hypertension, but those receiving hemodialysis had the highest frequency of PH (38.5%).

Both ESRD and long-term hemodialysis via arteriovenous access may be involved in the pathogenesis of PH by affecting pulmonary vascular resistance and cardiac output.

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INTRODUCTION:

Patients who have an end-stage renal illness or chronic kidney disease are more likely to have pulmonary hypertension (PH), which increases likelihood of hospitalization and mortality. Despite this, the relationship between PH and CKD is still unclear due to the scarcity of evidence.[1] According to various types of literature, echocardiography (ECG) is used to identify pulmonary hypertension among CKD patients, with most patients receiving a diagnosis of PH with no known underlying cause.[3]

PH is more prevalent in CKD patients with a prevalence of 40% requiring dialysis and PH demonstrates as the independent factor for predicting mortality. The primary contributing factor to the onset of pulmonary hypertension could be the hormonal or metabolic imbalance associated with CKD, which causes constriction of the pulmonary arteries and increase in pulmonary vascular resistance.[6] Additional causes such as increased oxidative stress or endothelial dysfunction from uremic toxins, and vascular calcification are the few postulated pathways that can result in the formation of PH in CKD however, there is no evident preclinical or clinical data to correlate the aetiology of PH in CKD. [11] PH is brought on by plexiform lesions, which result in the complete destruction of the lumen and vasoconstriction of the micro-vessels in the lungs, increasing flow resistance. The postulated theories for the origin of the lesion include angiogenesis response to local stimuli and the deregulation of endothelial maturation. CKD-related hormonal and metabolic alterations may result in vasoconstriction of pulmonary artery and an elevation in pulmonary vascular resistance. Excessive cardiac output brought caused by the arteriovenous route, as well as often frequent anaemia and fluid overload, can all worsen pulmonary artery pressure (PAP). [12]

Nitric oxide a vasodilator and thromboxane a vasoconstrictor, work in balance to control the localized vascular tone and performance of the pulmonary arteries. Hemodialysis (HD) does

not alleviate endothelial dysfunction in CRF patients because of poor nitric oxide activity. An increased neuronal natriuretic hormone is linked to ageing, left ventricular hypertrophy, kidney failure, and PH. A by-product of BNP known as N-terminal pro-brain natriuretic peptide (NT-proBNP) has shown to have predictive value in PH.[15]

AIMS & OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY:

To determine and compare the proportion of Pulmonary Hypertension among Chronic Kidney Disease patients on conservative management and on Hemodialysis.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

INTRODUCTION

PH is indicated by mean pulmonary artery pressure (PAP) higher than 25 mm Hg. PH is being diagnosed and detected more frequently. The prevalence of PH in general is between 10 to 20 per cent.[1] Any detection of PH, whether deliberate or unintentionally discovered on echocardiography or right cardiac catheterization, merits investigation into the cause, knowledge of pathophysiology, and consideration of available treatments. In USA, an estimated 3–4 million cases of left heart disease are exacerbated by PH. When right ventricular (RV) failure develops, there is a twofold increase in mortality risk.[2,3]

CKD which has a 13% prevalence in the developed world, is known to elevate the risk of cardiac problems as well as renal failure and other comorbidities.[4] End stage kidney disease (ESKD) significantly raises the probability of death, cardiac disease, and the need for specialized medical attention. In this setting, individuals with ESKD kept on long-term hemodialysis have been documented to have PH. The incidence of PH in these clinical groups is estimated between 17% to 56% based on echocardiographic (ECHO) investigations. In CKD patients, PH is a major predictor of morbidity and mortality. Most studies fail to distinguish between precapillary and postcapillary PH in randomly selected patients both with and without indications because of lack of invasive hemodynamic data.[5-10]

Reviewing the hemodynamic causes of PH and outlining the variety of ailments that might cause PH seems to be crucial to understanding this connection. The hemodynamic anomalies that results in PH are described by the formula for peripheral vascular resistance (PVR) derived from “Ohm's law which states that resistance equals to change in pressure divided by flow.” This equation is rearranged and simplified to highlight the pathogenic conditions that lead to high PAP.[11-13]

In typical clinical practice, the modified Bernoulli equation is used to estimate PAP during echocardiography: "PAP = 4 × (tricuspid systolic jet velocity)^2 + estimated right atrial pressure (RAP)" , usually calculated using a predetermined, fixed value or measured using vena cava diameter. [14-15]

One of the well-known limitations of ECHO in the specific diagnosis of PH is the difficulty in determining pulmonary tension when the tricuspid jet is difficult to discern or is tiny, as well as the dependence on indirect unreliable assessments of RAP. However, there are a number of factors why echocardiography is widely used to identify PH by surrogate estimates, including its higher accessibility contrasted to right heart catheterization, cost effectiveness, security of noninvasive measurements, and easy accessibility for screening. Despite the above advantages, the significance of the right catheterization for assessing PH in kidney disease patients cannot be emphasized as PH in ESRD/CKD is a complex process, and ECHO can only partially identify the precise role of pulmonary capillary wedge pressure (PCWP), PVR and cardiac output (CO) in assessing increase in PAP.[16-17]

CLASSIFICATION

Previously, pulmonary hypertension (PH) was classified into 2 classes based on the existence of known causal factors

1. Primary PH
2. Secondary PH

Pulmonary hypertension (Primary)

"PH is defined as a median pulmonary arterial tension of much more exceeding 25 mm Hg at relaxation or 30 mm Hg during activity." [19] Despite the fact that the illness has a wide range

of causes and classifications, pulmonary hypertension is typically categorized either as primary or secondary based on clinical criteria. A main pulmonary hypertension diagnosis is obtained once all other secondary pulmonary hypertension causes have been clinically eliminated.[20]

PPH was originally noted in a patient with RV heart failure more than a century ago, whose autopsy revealed no cause for pulmonary arteriosclerosis.[21] It was determined that the ailment was pulmonary arteritis due to syphylis. While Ayerza identified the considerable cyanosis related to the illness in 1901 and labelled it "cardiacos negros," the terminology primary pulmonary hypertension (PPH) was actually developed by Dresdale.[22] An outbreak of PH was blamed on the widespread use of the tonic aminorex fumarate throughout Europe in 1967. The sickness has received more attention as a result, leading to the organization of WHO conference and handbook on diagnosis and treatment. The US National Institutes of Health established a PPH registry in 1981 to better understand the natural history of the disease, and the International PPH Study Group defined the role of prescription drugs in the disorder in 1994. These drugs have been taken off the market in North America and Europe as a result of research into their negative effects, which include a link to cardiac valve defects. [23]

PPH affects 1-2 instances per million people annually, however necropsy investigations have showed that the prevalence is 1300 cases per million, according to research undertaken in Europe and the United States. Users of appetite suppressants may experience PPH at a rate of 25 to 50 million per year. Although PPH can be diagnosed at any age, the average age of presentation is a little older in men than in women, with an average of 36 years. There is female predominance in both juvenile familial PPH and adult disease (women/men ratio 17-35). The low life expectancy of male fetuses with PPH may help to explain the female advantage. Race has no impact on PPH risk.[24-27]

Pulmonary hypertension (Secondary)

Most hypertensive patients are classified as suffering from primary hypertension because the cause of their condition is typically from a known cause. Moreover, 5% to 10% of these individuals may have secondary hypertension, suggesting a root cause that may be treated. By age, secondary hypertension frequency and likely aetiologies change. The two frequent causes of mortality in youngsters being renal parenchymal disease and aortic coarctation. In people 65 and older, hypothyroidism, renal insufficiency, and atherosclerotic renal artery constriction are major causes. When there are warning signs and scientific proof, such as important or high resistance hypertension, starting age of fewer than 30 years (especially prior to actual puberty), malignant or instantaneous hypertension, and a sudden increase in blood pressure from previously stable readings, secondary high blood pressure should be identified and treated. [28]

Patients with severe hypertension who have a comparatively small kidney or difference in size of kidney more than 1.5 cm, frequent flash pulmonary oedema, or more than 1.5 times escalation of serum creatinine within one week of beginning angiotensin receptor blocker or angiotensin-converting enzyme inhibitor treatments have to be evaluated for renovascular hypertension. In addition, conditions like hyperaldosteronism, obstructive sleeping apnea, pheochromocytoma, Cushing syndrome, thyroid disease, aortic coarctation, and drug usage can result in secondary hypertension.[28]

Clinical classification of pulmonary hypertension[29]

1. **Pulmonary arterial hypertension**

1.1 Heritable PAH

1.2 Idiopathic PAH

1.2.1 BMPR2

1.2.2 Drug and toxin-induced

1.2.3 Unknown

1.3 ALK-1, ENG, SMAD9, CAV1, KCNK3

1.4 Associated with:

1.4.1 Schistosomiasis

1.4.2 congenital heart diseases

1.4.3 Portal hypertension

1.4.4 HIV infection

1.4.5 Connective tissue disease

1′ Pulmonary Veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1″. Pulmonary hypertension due to left heart disease

2. Persistent pulmonary hypertension of the newborn (PPHN)

2.1 Left ventricular diastolic dysfunction

2.2 Left ventricular systolic dysfunction

2.3 valvular disease

2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

3. Pulmonary hypertension due to lung diseases and/or hypoxia

3.1 Interstitial lung disease

3.2 Chronic obstructive pulmonary disease

3.3 Sleep-disordered breathing

3.4 Other pulmonary diseases with mixed restrictive and obstructive patterns

3.5 Chronic exposure to high altitude

3.6 Developmental lung diseases

3.7 Alveolar hypoventilation disorders

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear multifactorial mechanisms

5.1 Systemic disorders: sarcoidosis, pulmonaryhistiocytosis, lymphangioleiomyomatosis

5.2 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy

5.3 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

5.4 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders

The WHO in 1973 held a conference on PH, and in 1988 it proposed the Evian classification after devising a categorization system. The terminology primary pulmonary hypertension was changed in 2003 in Venice by the term idiopathic pulmonary arterial hypertension (IPAH). Another significant alteration made during the Venice meeting was the amalgamation of pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) into essentially a single category of PAH.[29]

PAH group 1 – Pulmonary arterial hypertension

Idiopathic and heritable PAH(IPAH) –

IPAH is a randomized illness with really genetic background and no recognized risk factors. Bone morphogenetic protein channel type 2 (BMPR2) gene mutations are present in around 70% of families with PH. The term "familial PAH" was dropped from the revised categorization and replaced with "heritable PAH" since no BMPR2 alteration has been found in 30% of populations with PAH. [30,31]

Drug and toxin-induced PAH–

D-PAH is a right heart failure that progresses to mortality and World Health Organization Group 1 pulmonary hypertension (PH) is characterised by significant microvascular loss and obstructive vasculopathy. D-PAH has been connected to 16 different compounds, including stimulants used for recreation and, more recently many drugs that have received FDA approval. The clinical outcome of D-PAH is unknown and depend on the removal of the drug, despite the fact that its clinical signs, histopathology, and hemodynamic profile are identical to those of other kinds of pulmonary arterial hypertension.[32]

Genetic susceptibilities are involved in the aetiology of D-PAH because it only affects a tiny proportion of the population; however, the genetic factors causing these susceptibilities have not been fully characterised. The primary challenge in managing D-PAHs is the early detection of chemicals that can harm pulmonary circulation in susceptible people, in addition to robust therapy with PH-specific drugs. [32]

PAH associated with connective tissue disease –

A common disorder that affects 1% of the community is congenital heart disease. This population's eventual PAH prevalence is 15%.[33] Eisenmenger's syndrome is a shunt from

right-to-left causing cyanosis and diminished endurance, is the most severe PAH condition is due to increase in pulmonary vascular resistance.[29]

The most common diseases related to PAH are connective tissue disorders (CTDs). The majority of CTD-PAH cases—roughly 75%—involve Systemic Sclerosis (SSc), the most common CTD aggravated by PAH. (8-12% of SSc patients). PAH is the major cause of death in SSc and has a worse prognosis than IPAH. Furthermore, 1-5% of persons with systemic lupus erythematosus (SLE) and 3-4% of people with mixed connective tissue disease(MCTD) have PAH. There have been few reports of CTD-PAH even in other CTDs. [34,35]

PAH associated with congenital heart disease(CHD) –

About 10% of adults with CHD have PH. Pre-capillary PH is referred as pulmonary arterial hypertension (PAH), a subset of PH patients. In people without additional precapillary pH causes, such as lung disease or persistent thromboembolic pulmonary hypertension, this is indicated by 15 mmHg of pulmonary artery wedge pressure and greater than 3 Wood Units pulmonary vascular resistance (PVR). [36]

About 5-10% of adult persons with CHD have PAH (CHD-APAH), which significantly affects mortality and morbidity and increases the need for ongoing care.[37]

According to a study based on epidemiology, 6.1% people with septal abnormalities had CHD-APAH, had an average lifespan of 38 years, and were 60% female. According to estimates, 15.6 people per million people had CHD-APAH, with Eisenmenger syndrome influencing 58% of those affected. A ventricular septal deficiency was also the most prevalent underlying abnormality, accounting for 42% of cases (VSD).[38,39]

Despite the existence of identical underlying cardiac abnormalities, the degree of CHD-APAH severity can differ significantly, highlighting the condition's dynamic character and

multiple origins. The deficiency itself is assumed to be the cause of CHD-APAH, but environmental factors, genetics, and epigenetics may also play a role. According to research, BMPR2 mutations are present in 6% of people with CHD-APAH and are also associated with idiopathic and hereditary PAH. PAH along with this is seen in mutations associated wih protein ALK-1.[40-42]

PAH associated with HIV infection -

About 0.5% of HIV patients have PAH. The development of antiretroviral therapy which has drastically improved survival are to account for the growth in PAH and non-infectious conditions of HIV infection. Clinically, immunosuppression does not appear to have an impact on HIV-associated PAH, which resembles IPAH. Recently, the prevalence of PAH linked to HIV was measured and discovered to be stable at 0.46%.[43,44]

Portal hypertension –

PAH due to portal hypertension is called as portopulmonary hypertension (POPH). 26% of sick people with portal hypertension have PH, according to prospective studies. Autoimmune hepatitis and the female sex have both been reported to be risk factors for POPH. Prognosis is influenced by cardiac function, cirrhosis prevalence and severity, and other factors.[45]

PAH associated with schistosomiasis –

Since 2008, the PAH related to schistosomiasis is categorised in group 1. This form of PH was included under group 4 previously. Schistosoma eggs were thought to block the pulmonary arteries, which led to PAH. Similar histopathological findings, such as plexiform lesions, are noticed in both IPAH and PAH related with schistosomiasis, according to recent articles. According to the most recent data,greater than 200 million people have contracted

one of the three Schistosoma species, and 48% of patients also have PH and hepatosplenic illness.[46,47]

PAH group 2 - Pulmonary hypertension due to left heart disease

Amonth the various causes of PH left heart failure (HF) is one of the common cause. In reality, left heart conditions account for 65–80% of cases of PH (LHD). Although there are targeted treatments for PAH, the drugs have not been well studied and may be harmful in sick people with PH brought on by HF. [48,49]

Confirming the class of PH is essential for making treatment decisions. However, there are serious discrepancies in practice that one should be cautious as individuals with PH and lone LHF are commonly misdiagnosed as having PAH and given medications specifically for that condition. Whereas patients with class 5 PH receive targeted therapy without being clearly identified. But it's often overlooked that HF frequently coexists with PH and RV dysfunction, each of which has a considerable impact on the disease's onset, morbidity, and death. However, the safety and effectiveness of a particular PH therapy are still unknown due to the complicated hemodynamic interactions.[50]

The frequency and severity of PH and RV HF are associated with disease progression, decreased sensitivity to exercise, and a poor prognosis, which is similar in LVHF. Depending on the PAP measurement methodology, the PH criteria, and the demographics examined, PH prevalence varies in HF patients. Despite the fact that both HFrEF and HFrEF share similar term of "heart failure," they are distinct conditions with their own pathogenesis, characteristics, hemodynamics, interactions with the heart and lungs, and responses to treatment. As a result, each should be treated separately. RHC estimates that between 40 and

75 per cent of HFrEF patients have PH.[3,51,52] Recent research in patients with HFpEF using either RHC or echocardiography reported a range of PH prevelance from 36 to 83%. [53]

Regardless of other existing predictors of outcome, PASP measured by ECHO in heart disease, strongly predicted mortality in a trial of HF patients. Multiple studies have shown a negative correlation in both PH and survival, in patients of HFrEF, a bad prognosis was particularly associated with a both combined elevated PAP and cognitive impairment systolic function of RV. Studies in HFpEF patients revealed a strong correlation between PH and mortality. Additionally, RV impairment, which is frequently seen in HFpEF is significantly linked to increased PAP, exists at later phases and is a main indicator of death.[3,53,54-56]

PAH group 3 – Pulmonary hypertension due to lung diseases and/or hypoxia

PH is a frequent side effect of lung disease. According to the most recent revisions to the classification of pulmonary hypertension, chronic lung diseases or pathologies with alveolar hypoxia fall under WHO Group III of PH-related diseases (PH). In this classification, the group's makeup remained largely unaltered. The title has lately been changed to reflect the progression of PH's cause and effect. The main modification was the introduction of a new classification of respiratory illness with a combined obstructive and restrictive sequence, that also includes chronic bronchiectasis, cystic fibrosis, as well as a disorder with a PH prevalence of almost 50% and a disease combination of pulmonary fibrosis and emphysema.[57,58]

Alveolar hypoxia is due to many causes, including mixed restrictive and obstructive respiratory diseases, chronic airway diseases, abnormalities in ventilatory control and, as a result, PH. Dyspnoea can be brought on due to both primary respiratory disease and PH, which is why the former is frequently disregarded. Data on the incidence of PH in each of these diseases is therefore lacking.[58,59]

The prevalence of COPD-related PH is influenced by heterogeneity, co-morbidities, assessment methods, and COPD development. In a retrospective observational analysis of about 4000 individuals with severe COPD waiting for lung transplants, PH prevalence was found to be 30.4%. Even though it may not be dependent on hypoxia, raised pulmonary artery pressure (PAP) is frequently seen in severe emphysema. But most prevalence studies did not use the gold standard for characterising PH, which is measuring PAP via right cardiac catheterization. Cystic fibrosis has been found to have a PH prevalence as high as 63%, characterised as median PAP of 25 mmHg.[60,61]

Chronic obstructive pulmonary disease –The incidence of PH in patients with COPD (COPD-PH) varies based on the severity of disease. The incidence of PH with COPD has also been connected to specific genetic markers. [62]

According to research, up to 90% of those with spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) phase 4 may have aberrant mPAP (>20 mmHg), with the majority falling between 20 and 35 mmHg. Only 1 per cent to 5 per cent of Patients with COPD have a resting mPAP greater than 35-40 mmHg.[63]

Majority of COPD experience sudden increase in mPAP even with light exercise, which is indicative of a failure of the elastic properties of the vasculature in the lungs. In people with COPD, PH can be brought on by concurrent left heart disease, sleep apnea, or chronic pulmonary thrombus formation. The majority of the time, moderately severe PH in COPD has no impact on right ventricular function.[64-66]

The main cause of PH in COPD is pulmonary vascular remodelling. At different stages of the disease's severity, it impacts tiny and precapillary arteries. The most obvious pulmonary vascular remodelling feature is the augmentation of intima in muscle arteries. Smooth muscle cell (SMC) proliferation-induced intimal hyperplasia produces bundles of longitudinal

musculature that are different from the usual circular position and accumulate elastic and collagen fibres. The arterioles develop a midline covering of circular smooth muscle surrounded by a fresh elastic layer.[67,68] Pulmonary muscular artery intimal hyperplasia is evident at all stages of the illness. Because they lack contractile filaments, a sign of mature cells, the majority of SMC that proliferate in hyperplasic intimas in moderately severe COPD have a poorly differentiated phenotype.[67]

Interstitial lung diseases (ILD) -PH in individuals with ILD are underdiagnosed and can happen even when there is no substantial hypoxemia or pulmonary dysfunction. The ILDs most typically associated with PH are connective tissue disease-related ILD, sarcoidosis, idiopathic pulmonary fibrosis, and pulmonary Langerhans cell histiocytosis. In individuals with ILDs, the consequences of PH are mostly overlooked that can impair functional capacity and lifespan.[69]

ILD patients may develop pulmonary vasoconstriction, vascular damage and remodelling brought on by parenchymal fibrosis, perivascular fibrosis, vascular inflammation and thrombotic angiopathy which are potential causes of pulmonary hypertension. Due to the vague clinical findings in these individuals, particularly when a parenchymal lung ailment is present, PH evaluation in these patients requires a high degree of suspicion.[69]

The right cardiac catheterization is essential to confirm the presence of PH and assess its severity. The evaluation of the underlying cause and the clinical setting dictate the treatment of PH in these patients. Newer pharmacologic drugs used in the management of PH make it possible to treat PH in these patients. It is necessary to evaluate whether specific PH treatment improves functional capacity or outcome in these patients.[69]

Sleep-disordered breathing - Sleep-related breathing disorders include central apnoea, disruptive apnoea and sleep-related hypoventilation (SBDs). SBDs have the possibility of

increasing PAP both while awake and while sleeping. PAP slightly rises in "pure" obstructive sleep apnea syndrome (OSAS). On the other hand, nocturnal respiratory episodes in obesity hypoventilation syndrome (OHS) or overlap syndrome (the combination of COPD and OSA) lead to progress of PH, which is often severe. In the second case, SBD therapy is required to enhance pulmonary hemodynamics.[70]

SBDs are more prone to form in patients with PAH or CTPH. Disruptive and central apnea, along with an exacerbating of the air circulation mismatch, may be observed while a person is sleeping. Although there should be a strong suspicion of SBDs in this patient population, the accurate predictors for sleep patterns and the method of recording must be established. Continuously positive airway pressure should be used to treat OSAS in sick people with PAH or CTEPH. Long-term oxygen therapy should also begin in the event of isolated nocturnal hypoxemia. In patients with persistent RHF, it is advised against diagnosing central apnea and Cheyne-Stokes respiration with responsive servo-ventilation due to the likelihood that these therapies will prevent PH worsening.[70]

Chronic exposure to high altitude -Alveolar hypoxia, which has well-known effects on the cardio-pulmonary network, including the emergence of pulmonary hypertension, is the most observable aspect of a high-altitude environment. High elevation pulmonary oedema (HAPE), a potentially fatal illness that develops at higher altitude in healthy individuals is caused in part by pulmonary hypertension brought on by excessively hypoxic pulmonary vasoconstriction. Although there is a compelling physiological justification for utilising vasodilators to prevent and treat HAPE, in-depth studies evaluating their effectiveness have not yet been carried out. Considering the medical knowledge with nifedipine in HAPE therapy in vulnerable persons, calcium-channel blockers are currently advised for pharmacological prophylaxis in patients with a documented history of recurrent HAPE.[71]

Right heart failure results from the remodelling of the pulmonary arteries brought on by chronic hypoxia, which also results in PH. Pulmonary hypertension at high elevations may potentially be caused by chronic heart diseases and lung disorders, thrombotic or embolic illnesses, as well as other conditions. They may be helpful in treating elevated pulmonary hypertension, according to substantial clinical experience with medications in the treatment of pulmonary arterial hypertension. They are beneficial in reducing pulmonary artery tension in high-altitude patients, according to small trials. There are currently no approved drugs to treat persistent PH at high altitudes.[71]

PAH Group 4 – Chronic thromboembolic pulmonary hypertension (CTEPH)

CTEPH is brought on by thrombosis of pulmonary arteries brought on by an untreated acute pulmonary embolism. CTEPH in patients with acute pulmonary embolism is rare and it seems to be around 2.3%. Ventilation/perfusion scintigraphy is used to evaluate patients who have CTEPH because detection of misaligned segment defects is a defining characteristic of the condition.[72]

Diagnosis of CTEPH is by digital reduction pulmonary angiography. The patient is next assessed for operability to determine whether or not pulmonary endarterectomy surgery will be successful in treating him or her. Whenever pulmonary endarterectomy is not an option, balloon pulmonary angioplasty and medications that target pulmonary arterial hypertension may be employed.[72]

PAH Group 5 – Pulmonary hypertension with unclear multifactorial mechanisms –

Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy -PH has developed as a notable side effect of several haematological

conditions, such as hemoglobinopathies, anomalies of the red cell membrane, chronic myeloproliferative diseases, and splenectomy. There are just a few investigations that use the standard diagnostic cardiac catheterization to systematically determine the prevalence of PH , except for those involving sickle cell disease. A thorough diagnostic investigation is necessary since the cause of PH in individuals with hematologic abnormalities is complex. The lack of high-quality information on the positives and negatives of PH-targeted therapy in this patient population is even more concerning.[73]

Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis - Pulmonary hypertension in sarcoidosis causes breathlessness and is linked to higher morbidity and death rates. Numerous factors, such as granulomatous inflammation that results in vascular involvement, fibrotic changes and LV failure, might contribute to sarcoidosis-associated pulmonary hypertension (SAPH). Numerous case studies have shown that the therapy of pulmonary hypertension is beneficial for some SAPH patients. In a randomised, placebo-controlled experiment, using bosentan for 16 weeks was linked to a noticeable difference in pulmonary artery pressure. Which individuals will benefit from treatment for pulmonary hypertension may be determined by future study.[74]

The common cystic lung ailment known as pulmonary Langerhans cell histiocytosis (PLCH) is strongly associated with cigarette smoking. Dendritic cells from PLCH patients have recently been found to contain triggering pathogenic changes in the mitogen-activated protein kinase pathway, firmly defining PLCH as an inflammatory myeloid neoplasm. When it comes to PLCH, each person's illness progression and the prognosis is very different, varying from clinical remission to PH and progression to respiratory failure.[75]

The current classification of PH places Lymphangioleiomyomatosis (LAM) under Group 5. (unclear multifactorial mechanisms). However, there is little data on how often PH is in

LAM. In LAM patient, PH is rare if present is often mild and associated with lung parenchymal damage. PH detection in LAM patients was greatly enhanced by carbon monoxide diffusion capacity.[76]

Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders -Type I glycogen storage disease has been connected to two cases of pulmonary hypertension (type I GSD). Before the beginning of pulmonary hypertension, Patient 1 had nutritional therapy, a nightly gastric drip injection, and zyloric therapy. In addition to receiving nutritional therapy, patient 2 underwent surgery to create a shunt seen between intestinal vein and inferior vena cava. Both patients died of pulmonary hypertension-related progressive heart failure despite multiple attempts at pharmaceutical therapy. In neither case was there any indication of a condition that would have contributed to pulmonary hypertension. The autopsy in Case 1 showed plexiform vascular anomalies together with vasoconstrictive pulmonary hypertension.[77]

GD type 1 is distinguished by unexplained variability in its phenotype. PH in GD is rare and it is unknown how it presents clinically, what causes it, or how it responds to therapy with enzyme replacement +/-vasodilators.[78]

Both hyperthyroidism and hypothyroidism alter cardiac contractility, myocardial oxygen uptake, cardiac output, hypertension, and systemic or pulmonary total peripheral resistance. These circulatory problems are typically always reversible when the underlying thyroid issue is found and treated. Pulmonary hypertension and thyroid disorders, particularly hyperthyroidism, have been related (PAH). Patients with this kind of PAH tend to be elderly individuals with toxic multinodular goitres. [79]

EPIDEMIOLOGY OF PULMONARY HYPERTENSION –

All ages can be affected by PH, and the global prevalence is currently estimated to be around 1%. Left heart disease (LHD) is the main contributing factor, followed by lung conditions, especially chronic obstructive pulmonary disease (COPD).[80] Other common causes of PH in developing countries include congenital heart disease, viral illnesses (schistosomiasis, human immunodeficiency virus), and higher elevations. The prevalence of PAH in adults is 49–55 cases per million. It was previously believed to affect young girls, but current data suggests that it is now being discovered in individuals over the age of 65 who typically have cardiovascular issues, bringing the gender distribution closer to parity.[81]

At least 50% of people with heart failure and a preserved ejection fraction have IpcPH or CpcPH. The prevalence of PH increases with disease severity in these patients, affecting 60–70% of those with extensive mitral valve failure and 50% of those with symptomatic aortic stenosis. Patients with severe COPD and interstitial lung problems frequently experience mild PH (ILD). Only 1% to 5% of patients with advanced COPD were found to have severe PH. The prevalence of idiopathic pulmonary fibrosis rises with sickness severity and can approach 60% in those who are at the conclusion of their treatment. According to registry data, the prevalence and frequency of chronic thromboembolic pulmonary hypertension (CTEPH) predicted to be 2–6 and 26–39 cases per million people, respectively. Patients with sarcoidosis frequently get PH, which is linked to increased mortality and morbidity.[82-84]

ETIOLOGY OF PULMONARY HYPERTENSION –

Genetic changes are connected to several types of PH, including heritable PAH (HPAH), idiopathic PAH (IPAH), and hereditary hemorrhagic telangiectasia (HHT) connected to PAH. Patients with IPAH have a hereditary tendency with sporadic mutations, but those with

HPAH have had an inheritable genetic mutation, and these groups are clinically equivalent. BMPR2 (the most common), SMAD1, SMAD 9, KCNK3, CAV1, and SOX17 are among the IPAH/HPAH mutations. HHT mutations comprise ALK1, ENG, and SMAD4. [85]

The drugs/toxins that have been shown to cause PAH include aminorex, fenfluramine, dexfenfluramine, benfluorex, methamphetamines, dasatinib, and toxic rapeseed oil. Some substances/toxins that may result in PAH include cocaine, phenylpropanolamine, L-tryptophan, St. John's wort, amphetamines, interferon - and -, alkylating agents, bosutinib, direct-acting antivirals for hepatitis C, leflunomide, and indirubin. Systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Raynaud's syndrome, and mixed connective tissue disease are among the connective tissue disorders (CTDs) that contribute to PAH. The most well-known of them is systemic sclerosis, which causes PAH.[86,87]

The four kinds of PH linked to CHD are Eisenmenger syndrome-causing CHD, frequent systemic-to-pulmonary shunts, small/coincidental defects, and post-defect therapy PAH (PH-CHD). While most cases of PH-CHD fall under the classification of Group 1 PAH, some anomalies that result in mitral valve disease, LV obstruction or LV systolic/diastolic inefficiency may also cause post-capillary PH and are therefore classified as Group 2. [86,87]

While hypoxia without hypoventilation is found at high altitudes, group 3 hypoventilation syndromes encompass conditions that lead to sleep-disordered breathing. Sarcoma, other malignant tumours like renal carcinoma, uterine carcinoma, testicular germ cell tumours, and nonmalignant tumours like leiomyoma, arteritis without connective tissue disease, congenital pulmonary artery stenoses, and hydatidosis are other causes of PH in Group 4 patients besides chronic thromboembolic disease.[86,87]

Examples of haematological conditions that result in PH in group 5 include chronic hemolytic anaemia and myeloproliferative disorders. Systemic conditions such pulmonary

Langerhans cell histiocytosis, neurofibromatosis type 1, and sarcoidosis can lead to PH. Metabolic anomalies such Gaucher disease and illnesses affecting glycogen storage can lead to PH.[86,87]

DIAGNOSTIC EVALUATION

Chest radiograph -Although minor cardiomegaly, minor COPD, or minor ILD cannot be detected by chest radiography, the results are almost always accurate when any of these conditions is present with moderate to severe symptoms. A chest Computed tomography is the next step if result is borderline of normal or if a conclusive diagnosis is difficult to make as it is more precise and sensitive than radiography. The specificity and specificity of chest radiography anomalies are insufficient to make a definitive diagnosis of PH, notwithstanding the possibility that it exists. The following relevant chest radiography characteristics may indicate the existence of pulmonary hypertension: Increased diameter of main pulmonary arteries, hilar protrusion, trimming of the peripheral pulmonary arteries, inflammation of the right interlobar artery, enlargement of the right side of heart and areas of oligemia.[88]

Calculating pulmonary venous pressure can be done using PCWP, which reveals stress on the left side of heart. PCWP can be assessed on chest radiographs by looking at the vascular pattern and whether or not there is interstitial or alveolar oedema. PCWP values more than 13 mm Hg but less than 18 mm Hg may signify vascular redistribution in upper lung fields; values between 18 and 25 mm mm Hg may signify interstitial pulmonary oedema; and values over 25 mm Hg may signify alveolar oedema and, in some circumstances, pleural effusions. When certain clinical diseases show signs of pulmonary hypertension, left ventricular collapse should be strongly examined as a potential cause.[89]

Echocardiography - PAP gradually increases due to pulmonary vascular disease, which ultimately leads to right ventricular cardiac failure and death. ECHO or Right-heart

catheterization must be utilised to gauge the pulmonary artery systolic pressure(PASP) in order to make the diagnosis of PH . However, these methods might not be employed until a clear diagnosis is desired. Right ventricular hypertrophy (RVH), which is symptomatic with PH, is seen on the ECG. The criteria established by Myers and Sokolow serve as the foundation for much of the present RVH ECG criteria.[90-92]

These criteria largely depend on the right precordial leads, specifically an elevation in R wave, a decrease in S wave depth, and an increase in the RS ratio. The said theories responsiveness ranges from 0.5 to 40% despite having a high specificity of 90 to 100%.[93,94]

A high frequency Doppler of the tricuspid regurgitant jet or the parasternal RV inflow perspective if the regurgitant jet is asymmetrical, can be used to determine TRV, which represents the difference in pressure between the chambers of right side of heart. The RV systolic pressure (RVSP), which can be calculated from the TRV using the "Bernoulli's equation [PASP = (4 x TRV squared) + RAP]" and an approximation of pressure using the diameter of inferior vena cava, is thought to be the same as the systolic pressure where TRV end is the peak TRV at end-diastole in the absence of pulmonary stenosis. One major characteristic of ECHO in its function as a tool for diagnosis is the capacity to estimate systolic pressure, however, this comes with restrictions and there is a risk.[95]

Despite a significant correlation between the readings, Fisher et al. found that in more than 50% of patients, a difference of 10mmHg was seen between echo and cardiac catheterization. Underestimating systolic Ppa frequently leads to misdiagnosis of the severity of PH or even the inability to recognize PH.[96]

Inadequately enveloping the probe during ECHO results in an underestimation of pressure or an overestimation of pressure due to the diameter and collapsibility of the inferior vena cava were the most common causes of inaccurate systolic pressure calculations. In cases of severe

free-flow tricuspid regurgitation, the Bernoulli equation cannot be applied because TRV will overstate the trans-tricuspid differential pressure. Regardless of the underlying condition or systolic pressure, the degree of tricuspid regurgitation alone predicts survival.[96,97]

Right heart catheterization –RHC is considered the gold standard to estimate pulmonary hemodynamics and for establishing PH diagnosis and defining the level of hemodynamic dysfunction. The definition of PH, which is solely based on invasive hemodynamics, is mPAP greater than or equivalent to 25 mm Hg by RHC assessed at rest. Given that the upper range of normal for mPAP is 20 mmHg, the relevance of and clinical significance of readings around 21 and 24 mmHg are still up for debate.[98] Precapillary PH is indicated by a pulmonary artery wedge pressure (PAWP) that is less than or equal to 15 mm Hg, and postcapillary PH is indicated by a PAWP more than 15 mm Hg. Depending on whether the pulmonary vascular obstruction (PVR) is less than or equal to 3 Wood units and/or the diastolic pulmonary gradient (DPG) is less than or equal to 7 mm Hg, postcapillary PH is either classified as isolated postcapillary PH (Ipc-PH) or consolidated postcapillary and precapillary PH (Cpc-PH) (WU). The purpose of DPG is still up for debate, though. In the absence of other causes of precapillary pHs, such as PH brought on by lung diseases or persistent thromboembolic PH, precapillary PH with PVR more than 3 WU are signs of PAH. The requirements for coupled postcapillary and precapillary PH are DPG greater than or equivalent to 7 mm Hg and/or PVR greater than 3 WU (Cpc-PH).[98]

Appropriate classification must be performed utilising invasive procedures for the treatment of PH patients. The clinical presentation and imaging results must always be taken into account while evaluating invasive hemodynamics. RHC is a difficult procedure and necessities expertise, concentration and meticulous data gathering. In order to generate accurate and repeatable outcomes and reduce the hazards associated with the treatment, RHC

must only be carried out by professionals with experience and training in this specific technique and condition. [99]

PH IN CRF –

Both CKD and ESRD patients develop PH. More importantly, CKD patients who have PH are at an increased risk of hospitalization and mortality.[100-102]

Despite the significance of PH for prognosis, it is not known how common PH is in CKD. Most previous studies estimating the frequency of PH in CKD relied on echocardiography, which is frequently inaccurate, to diagnose PH.[103]

Additionally poorly known is the pathophysiology of PH in CKD. There could be many different systems at work. Because of this, PH caused on by CKD and ESRD is now classified by WHO as being caused by "other factors," or WHO group 5 . Left heart dysfunction, thromboembolic disease, autoimmune diseases such scleroderma and systemic lupus erythematosus, and liver and lung abnormalities are commonly present in CKD patients, all of which are recognised risk factors for PH. It has been proposed that PH and pulmonary vascular remodelling may occur on their own in CKD patients, especially ESRD.[104]

Some of the postulated potential pathways include increased flow from arteriovenous fistulas, vascular calcification, endothelial dysfunction introduced on by enhanced oxidative stress from uremic toxins, inflammatory reaction brought on by blood exposure to dialysis membrane, and vascular calcification .[104]

The approximate glomerular filtration rate was used to assess renal function by the CKD-EPI creatinine equation. Those with stage 2 or less renal impairment were excluded, and only those with stage 3 or higher stages of CKD were taken into consideration for the study.[104]

The electronic health record was used to obtain clinical, laboratory, and hemodynamic data. ICD-9 codes, which are used to classify diseases internationally, are used to define co-morbidities. Exclusion criteria included long-term thromboembolic illness, acute myocardial infarction, CHD and previous cardiac or lung transplantation. Using the Social Security death index, vital statistics were gathered.

68% of the patients in this group had PH, which is indicated by an average mPAP of 25 mmHg. Precapillary PH was more common (76% vs. 24%, respectively) than post-capillary PH. Post-capillary PH is defined as a PCWP of more than 15 mmHg or a mPAP of 25 mmHg. People with CKD who are young, African Americans, diabetic, overweight, have sleep apnea, left heart disease, scleroderma and COPD are more likely to develop PH. Despite most of the patients with pre-capillary PH had chronic hypoxic lung illness, cirrhosis, HIV infection, scleroderma and systemic lupus erythematosus, 58% of patients having pulmonary vascular disease have no known risk factors. After modifying risks for PH, it was discovered that having CKD had a 1.4 fold greater risk of the condition. Not least, in keeping with past research. If patients had PH, they had a higher mortality risk for stage 3 or worse CKD.

There are several noteworthy features of this study. The incidence of PH in CKD seen is much higher (68% vs. 30–40%) compared to earlier studies, to start.[100] Referral bias makes it likely that this estimate is too high. The authors exclusively examined CKD patients advised to have cardiac catheterization in a higher centre rather than studying all patients. Patients experience aberrant PAPs as a result of a clinically warranted RHC. Therefore, these prevalence findings could not apply to all CKD patients.[100]

Second, approximately 1/2 the individuals with precapillary PH in the study were female and had no established potential risks for vascular remodeling of the lungs. The majority were

female. Hence, the authors proposed that PH and CKD have a causal, sex related pathophysiological relationship and that CKD may cause vascular disease of the pulmonary vessels. In the study, ICD codes from computerised medical data were used to identify the risk factors for PH. This strategy is less precise than prospective registries. Therefore, it's likely that a PH potential risk were missed. Furthermore, if PH and CKD share a strong pathophysiological link, pre-capillary PH prevalence should increase as CKD severity increases. The study showed incidence of worsening post capillary PH with ESRD. There is also possibility of patients having either idiopathic or inherited PH and as a consequence of right heart failure, developed CKD, even if this patients have mild pulmonary vascular disease. The inadequate vascular compliance causing increase in pulse pressure hastens the progression of renal illness.[105,106]

An early sign of PH is decreased pulmonary vascular compliance. Decreased vascular compliance may be one pathological alteration that both CKD circulations share. Pre-capillary PH seems to be more prevalent in CKD.[107]

METHODOLOGY

MATERIALS AND METHODS

STUDY DESIGN: Cross sectional analytical study

SOURCE OF DATA: "This study will be conducted in the Department of General Medicine, R.L. Jalappa Hospital, Kolar."

STUDY PERIOD: Jan 2021 to Dec 2022

"INCLUSION CRITERIA:

CKD patients on HD or conservative management were selected.

CKD patients due to all etiologies and patients of all age groups were selected.

EXCLUSION CRITERIA:

COPD

Parenchymal Lung Disease

Chest Wall Disease

Previous history of PHT

Previous pulmonary embolism

Smoker (>5 pack years)

Collagen Vascular Disease

LV EF <50%

Significant mitral/aortic valve disease

Study Population

Patients diagnosed with chronic kidney disease presenting to

R L JALAPPA HOSPITAL during a time period of 6 months were included in the study afterthe application of inclusion and exclusion criteria.

STATISTICAL ANALYSIS:

Data will be entered into a Microsoft Excel Data Sheet and will be analyzed using SPSS 22 version software. Categorical data will be represented in the form of Frequencies and proportions. Chi-square will be used as test of significance. Continuous data will be represented as mean and standard deviation. p value <0.05 will be considered as statistically significant.

Graphical representation of data:

MS Excel and MS word will be used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots.

Pearson correlation or Spearman's correlation will be done to find the correlation between two quantitative variables and qualitative variables respectively.

P value: (Probability that the result is true) of <0.05 will be considered as statistically significant after assuming all the rules of statistical tests.

SAMPLING PROCEDURE:

After receiving institutional ethical clearance , the study was started.

Patients were explained about the procedure and their consent was taken and they were subjected to blood investigations and carotid Doppler.

Clinical, laboratory and sociodemographic data was elicited and recorded in a predefined proforma

1.Socio demographic data

Age

Gender

2.Clinical data

Height

Body weight

Clinical examination

BMI

3.Laboratory data

Two groups of patients were created using a computer generated random table.

Group A: Consists of 39 patients of chronic kidney disease and end stage renal disease undergoing hemodialysis correlated with pulmonary hypertension and results were analysed separately.

Group B: Consists of 39 patients of chronic kidney disease on conservative line of management correlated with pulmonary hypertension and results were analysed separately.

Investigations:

ECHOCARDIOGRAM

CBC

eGFR USING MDRD EQUATION

RENAL FUNCTION TEST

ECG

RESULTS

\

1. Characteristics of the patients

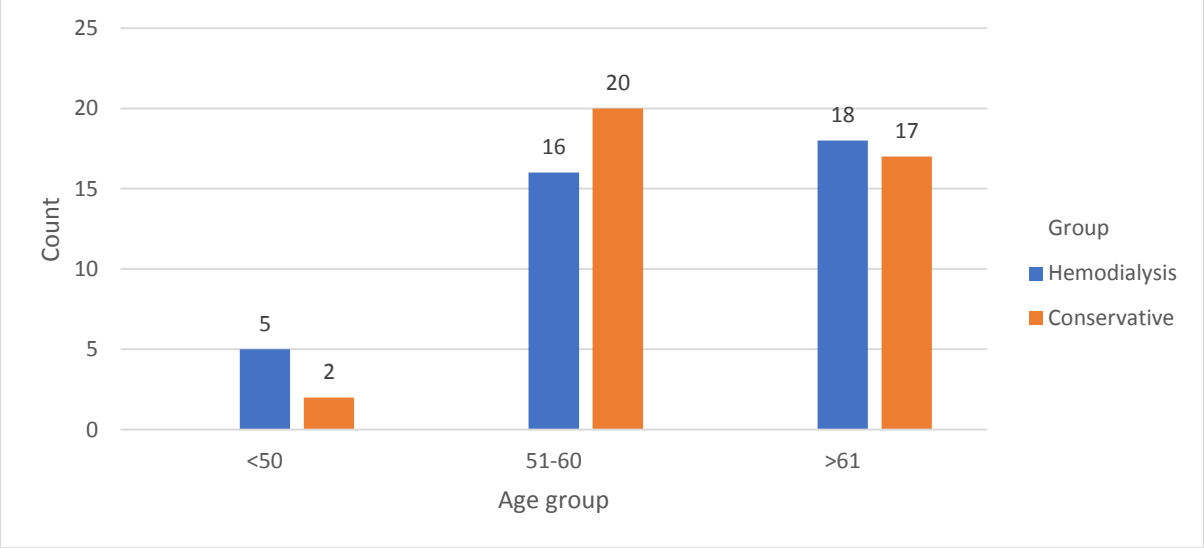
a. Age distribution

The current study included 78 patients in total, with the age group of 51 to 60 years old having a greater prevalence with 46.2% of the participants, followed by the age group >61 years (44.9%) (Table 1). Patients were further stratified into two major groups; hemodialysis and conservative group with 39 patients in each group respectively.

Table 1 – Age distribution in patients

			Group		Total	P value
			Hemodialysis	Conservative		
Age group	<50	Count	5	2	7	0.415
		% within Group	12.8%	5.1%	9.0%	
	51-60	Count	16	20	36	
		% within Group	41.0%	51.3%	46.2%	
	>61	Count	18	17	35	
		% within Group	46.2%	43.6%	44.9%	
Total		Count	39	39	78	
		% within Group	100.0%	100.0%	100.0%	

Figure 1 – % age distribution and group classification



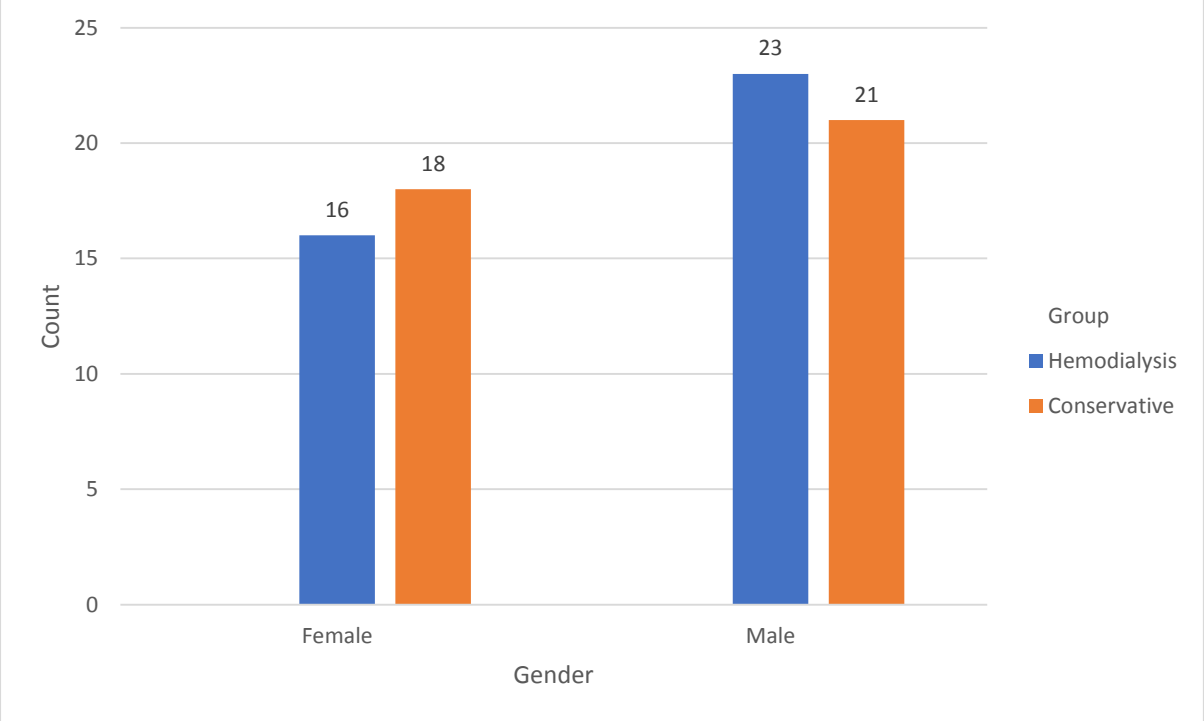
b. Gender distribution

The current study reports a male predominance with 56.4% of the total study participants however, 23 males and 21 males were included in the hemodialysis and conservative method respectively (Table 2).

Table 2 – Gender distribution

			Group		Total	P value
			Hemodialysis	Conservative		
Gender	Female	Count	16	18	34	0.648
		% within Group	41.0%	46.2%	43.6%	
	Male	Count	23	21	44	
		% within Group	59.0%	53.8%	56.4%	
Total		Count	39	39	78	
		% within Group	100.0%	100.0%	100.0%	

Figure 2 – % Gender distribution



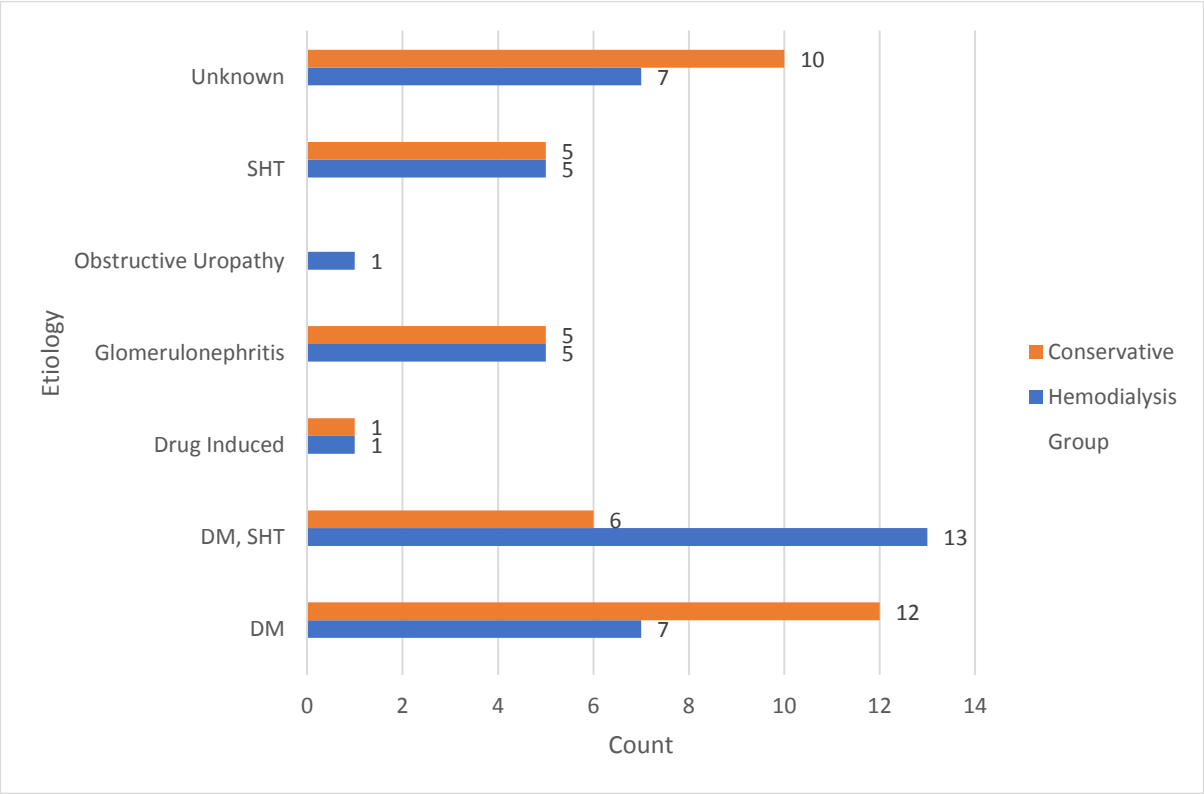
2. Etiology of patients

Our study included more patients with diabetes mellitus comprising of 24.4% of total participants, followed by diabetes and systemic hypertension among 24.4% of total patients. Unknown etiology for chronic kidney disease was reported in 17 patients (21.8%), followed by systemic hypertension in 10 patients (12.8%), and glomerulonephritis in 10 patients (12.8%). Drug-induced chronic kidney disease or renal failure was reported in 2 patients (2.6%) and obstructive uropathy was seen in 1 patient (1.3%) (Table 3).

Table 3 – Etiology of CKD

			Group		Total	P value
			Hemodialysis	Conservative		
Etiology	DM	Count	7	12	19	0.491
		% within Group	17.9%	30.8%	24.4%	
	DM, SHT	Count	13	6	19	
		% within Group	33.3%	15.4%	24.4%	
	Drug Induced	Count	1	1	2	
		% within Group	2.6%	2.6%	2.6%	
	Glomerulonephritis	Count	5	5	10	
		% within Group	12.8%	12.8%	12.8%	
	Obstructive Uropathy	Count	1	0	1	
		% within Group	2.6%	0.0%	1.3%	
	SHT	Count	5	5	10	
		% within Group	12.8%	12.8%	12.8%	
	Unknown	Count	7	10	17	
		% within Group	17.9%	25.6%	21.8%	
Total		Count	39	39	78	
		% within Group	100.0%	100.0%	100.0%	

Figure 3 – Etiology of CKD in patients



3. Duration and method of dialysis

A mean duration of dialysis was reported with 6 months ± 2.3 SD. Further to this the AV fistula method was used in a total of 22 patients (56.4%), followed by IJV catheter in 14 patients (35.9%), and permanent catheter in 3 patients (7.7%) (Table 4).

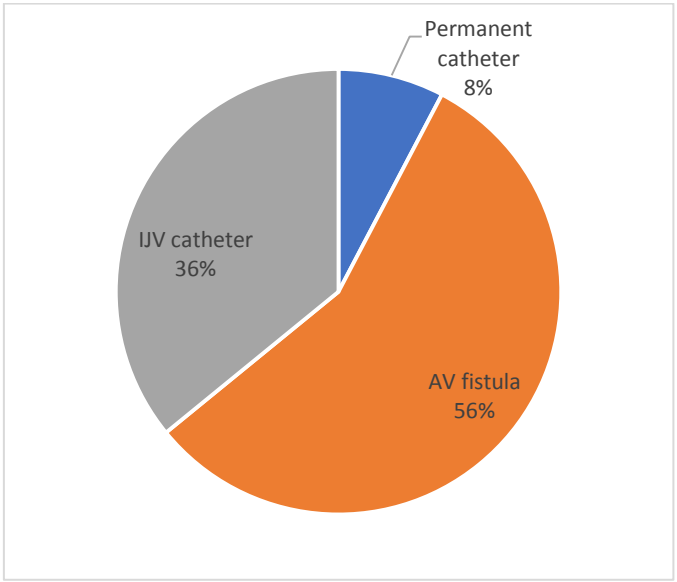
Table 4 – Mean duration of dialysis

	Mean	Std. Deviation
Duration of Dialysis (months)	6	2.3

Table 5 – Method of dialysis

Hemodialysis	Frequency	Percentage
Permanent catheter	3	7.7%
AV fistula	22	56.4%
IJV catheter	14	35.9%

Figure 4 - % distribution of dialysis method



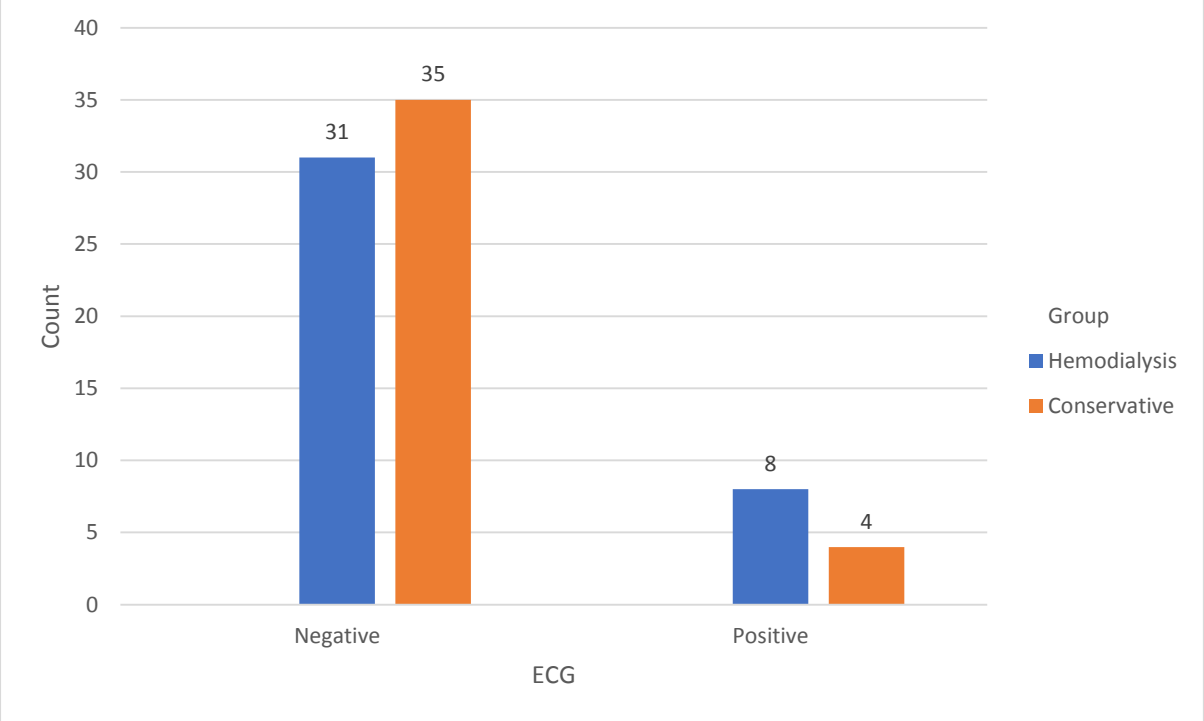
4. ECG comparison in patients

The study revealed no significance in both groups (hemodialysis and conservative) when assessed for ECG changes (p-value 0.209). However, 4 patients in the conservative group and 8 patients in the hemodialysis group both had favourable ECG changes. (Table 6).

Table 6 – ECG changes in patients

			Group		Total	P value
			Hemodialysis	Conservative		
ECG	Negative	Count	31	35	66	0.209
		% within Group	79.5%	89.7%	84.6%	
	Positive	Count	8	4	12	
		% within Group	20.5%	10.3%	15.4%	
Total		Count	39	39	78	
		% within Group	100.0%	100.0%	100.0%	

Figure 5 – ECG changes comparison both the groups



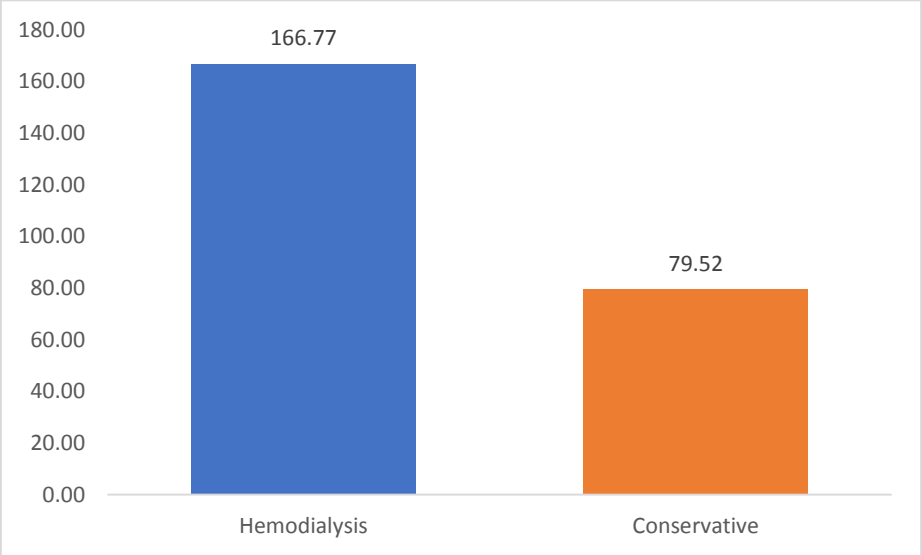
5. Serum urea comparison in patients

The study reports a significant difference in the urea levels in both groups (p-value <0.0001, which demonstrates a high level of serum urea among the hemodialysis group (Table 7).

Table 7 – Urea levels in patients

Group		Mean	Std. Deviation	P value
Urea	Hemodialysis	166.77	29.35	<0.0001
	Conservative	79.52	10.10	

Figure 6 – Urea level comparison



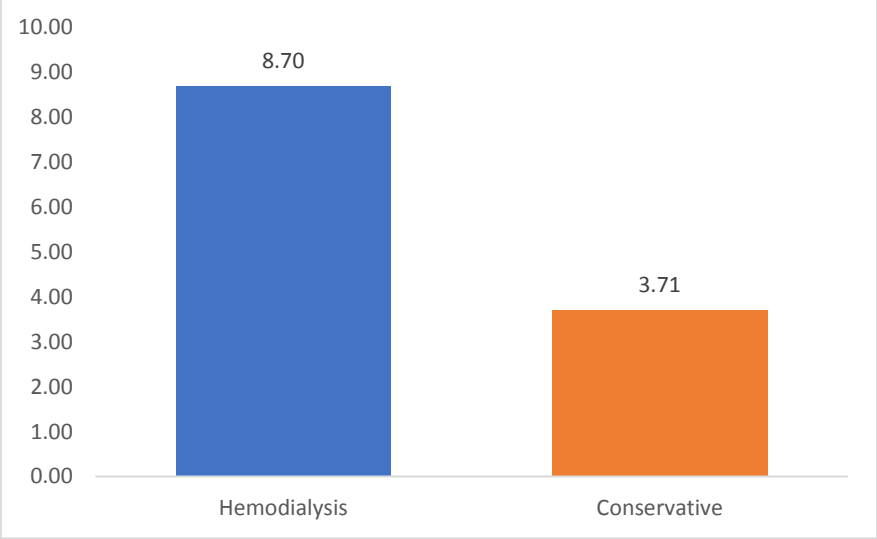
6. Serum creatinine levels comparison

The study finds a significant difference in the serum creatinine levels (p-value <0.0001) in the hemodialysis group (mean 8.70 ± 1.32 SD) and conservative group (mean 3.71 ± 1.12 SD) (Table 8).

Table 8 – Serum creatinine in patients

Group		Mean	Std. Deviation	P value
Creatinine	Hemodialysis	8.70	1.32	<0.0001
	Conservative	3.71	1.12	

Figure 7 – Serum creatinine level comparison



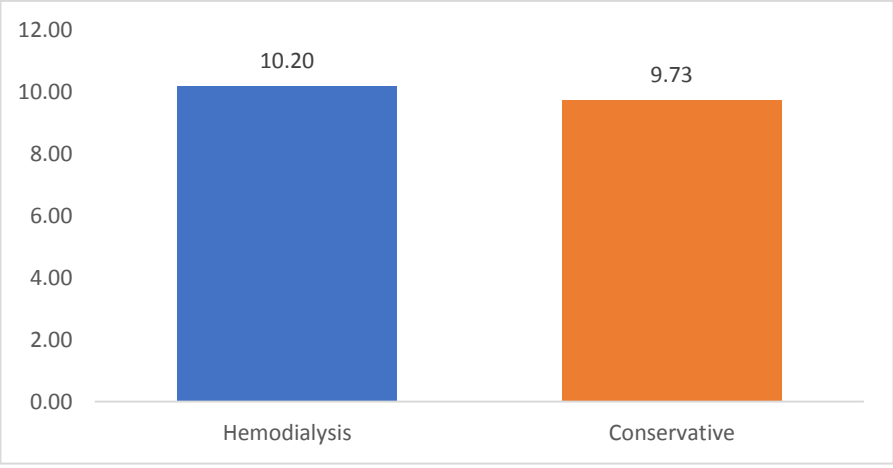
7. Serum hemoglobin levels

No significance between the hemoglobin levels in both groups was found in this study; however, the hemodialysis group recorded a mean of 10.20 ± 1.88 SD and the conservative group recorded a mean of 9.73 ± 178 SD (Table).

Table 9 – Serum hemoglobin levels in patients

Group		Mean	Std. Deviation	P value
Hb	Hemodialysis	10.20	1.88	0.259
	Conservative	9.73	1.78	

Figure 8 – Serum hemoglobin levels in patients



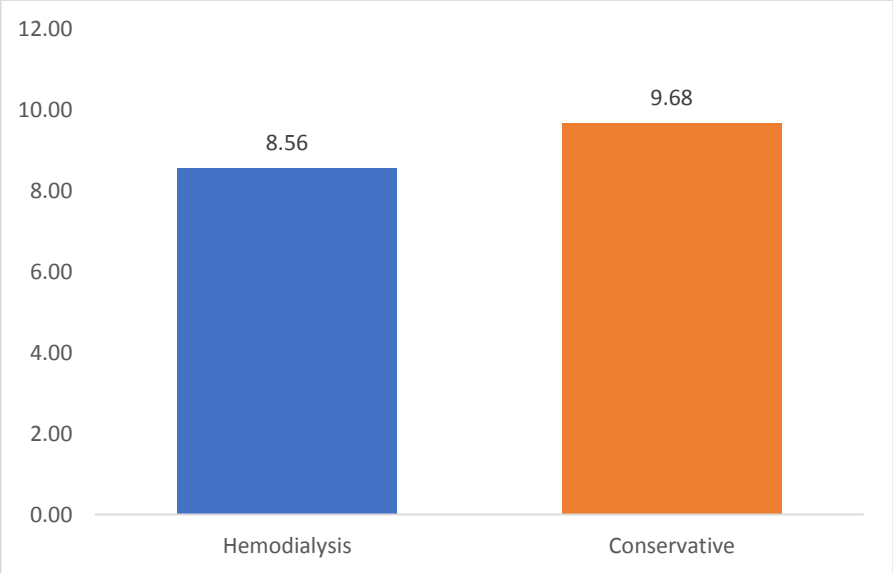
8. Serum calcium levels in patients

The study reports a significant difference in the group with serum calcium levels (p-value = 0.021). The hemodialysis group reported a mean calcium level of 8.56 ± 2.05 and the conservative group with a mean of 9.68 ± 2.11 (Table 10).

Table 10 – Serum calcium levels in patient

Group		Mean	Std. Deviation	P value
Calcium	Hemodialysis	8.56	2.05	0.021
	Conservative	9.68	2.11	

Figure 9 – Comparison of serum calcium levels



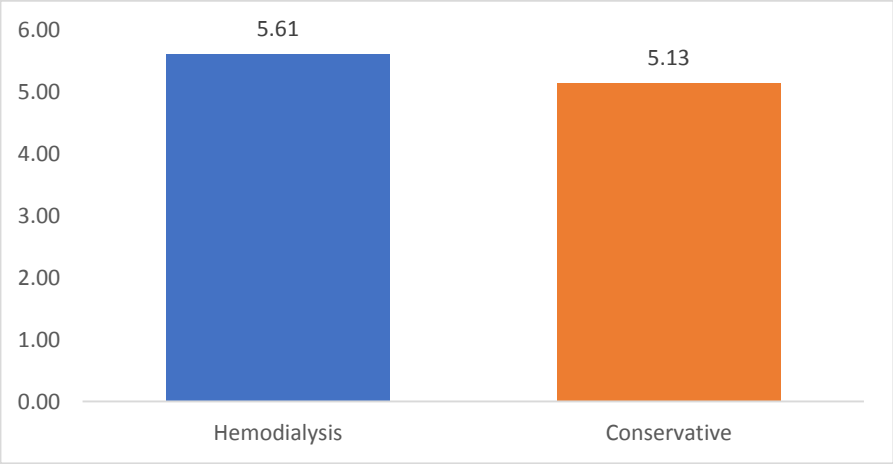
9. Serum phosphorus levels

In the current study no significant difference in serum phosphorus level comparison between the hemodialysis and conservative group was found (p-value = 0.289) (Table 11).

Table 11 – Serum phosphorus level comparison

Group		Mean	Std. Deviation	P value
Phosphorus	Hemodialysis	5.61	1.07	0.289
	Conservative	5.13	1.74	

Figure 10 – Serum phosphorus level comparison



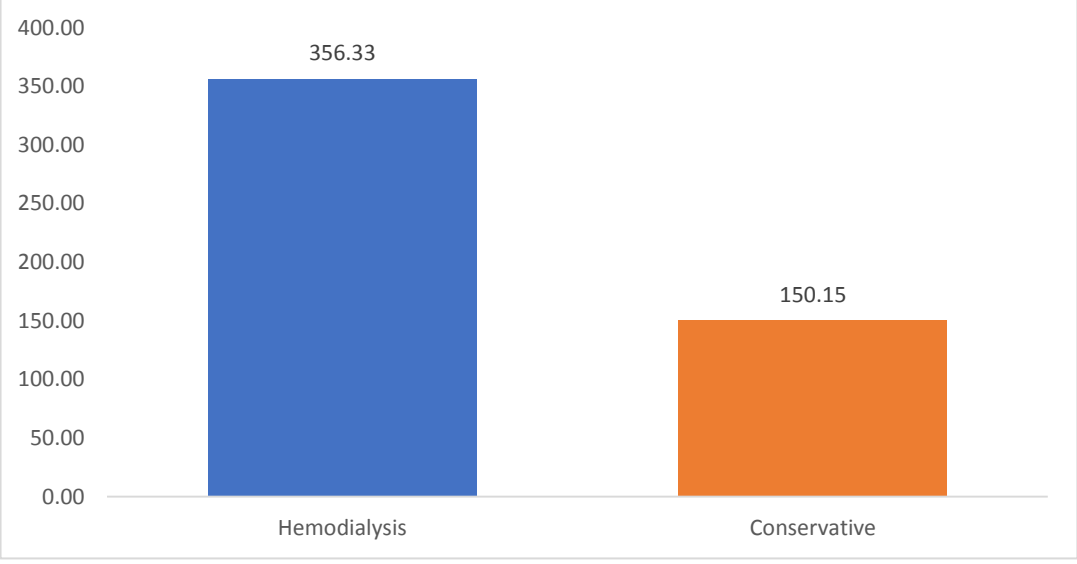
10. Alkaline phosphatase levels comparison

A significant difference between the serum Alk.phosphatase levels were reported in the current study where the hemodialysis group reported a mean serum alkaline phosphatase level of 356.33 ± 29.03 SD and the conservative group reported a mean of 150.15 ± 9.47 SD with a p-value <0.0001 (Table 12).

Table 12 – Serum Alk. Phosphatase levels in patients

Group		Mean	Std. Deviation	P value
Alk Phosphatase	Hemodialysis	356.33	29.03	<0.0001
	Conservative	150.15	9.47	

Figure 11 – Serum Alk. Phosphatase level comparison



11. Pulmonary hypertension (PHT) comparison

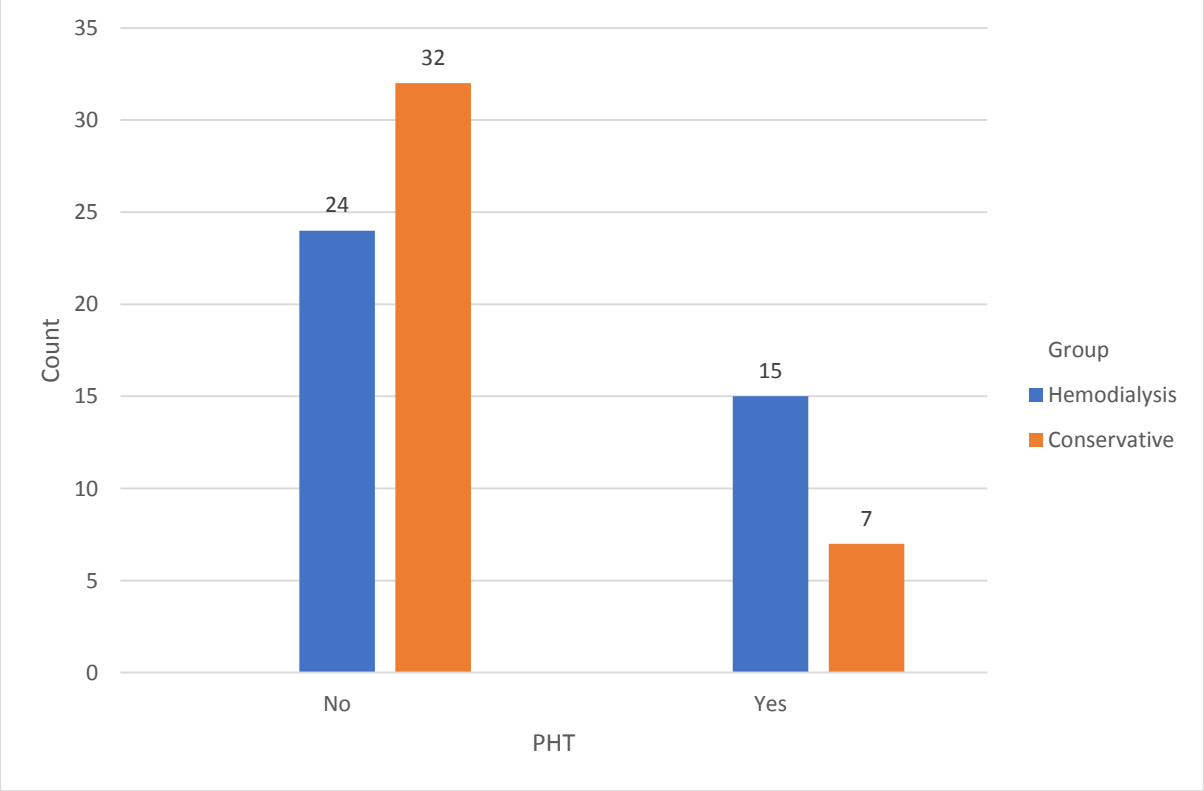
The current study indicates a substantial difference in PHT between the groups receiving hemodialysis and those receiving conservative treatment (p-value 0.044). The prevalence of

PHT was 38.5 percent in 15 patients receiving hemodialysis, compared to 17.9 percent in 7 patients on conservative treatment (Table 13).

Table 13 – PHT comparison

			Group		Total	P value
			Hemodialysis	Conservative		
PHT	No	Count	24	32	56	0.044
		% within Group	61.5%	82.1%	71.8%	
	Yes	Count	15	7	22	
		% within Group	38.5%	17.9%	28.2%	
Total		Count	39	39	78	
		% within Group	100.0%	100.0%	100.0%	

Figure 13 – PHT comparison in hemodialysis and conservative group



DISCUSSION

DISCUSSION:

According to estimates, 13% of people in industrialised countries have CKD, which is correlated with an increased risk of cardiovascular problems and a increased likelihood of renal failure. ESRD which is considered to be a high-risk factor for the emergence of PH and considerably raises the risk of disease progression. According to studies, ESRD patients have a significantly higher incidence of pulmonary hypertension.[108,109]

However, during an epidemiologic analysis, Yigla et al. confirmed the prevalence of initially unexplained PH in hemodialysis patients.[110] According to the literature, ESRD and long-term hemodialysis can both affect cardiac output and pulmonary vascular resistance, which may contribute to the aetiology of pulmonary hypertension.[111]

High cardiac output caused by arteriole-venous access, which is typically impacted by anaemia and fluid overload, may further raise pulmonary arterial pressure. As a result, the study's objectives included determining the prevalence of PH in CKD patients with and without dialysis as well as contrasting patient features in terms of their clinical, hemodynamic, and metabolic profiles.

In our study 22 patients (28.2 percent) of the total participants who had CKD had pulmonary hypertension, which was seen in both groups of patients. Of the total number of PH patients, 15 (38.5%) were treated with hemodialysis, whereas 7 (17.9%) were managed with conservative therapy. Patel et al. observed a comparable prevalence of PHT, with 41 patients reporting PHT, 33 percent of whom were on hemodialysis.[112] Furthermore, Mahdavi-Mazdeh et al. observed similar findings, with PH prevalence ranging from 30-40% in chronic hemodialysis patients.[113]; Abdelwhab and Elshinnawy found PHT in 44.4 percent of hemodialysis patients and 32.3 percent in the conservative care group.[114] With a p-value of 0.044, the current study also has a significant difference between the groups receiving

hemodialysis and those receiving conservative care, with the hemodialysis group having a greater prevalence of PH (38.5%).

The age group between 51-60 years of age was most prevalent with CKD and undergoing hemodialysis or conservative management (46.2%), followed by the age group >61 years (44.9%) with a male predominance (56.4%). However, no significant differences were reported. Magdy et al. similarly reported a similar conclusion, with the mean patient age in the hemodialysis group being 45.72±7.83 SD and the mean patient age in the conservative care group being 45.45±3.77 SD. [115]

Patients with CKD were majorly presented with a comorbid condition such as diabetes mellitus (24.4%), followed by both diabetes and hypertension (24.4%) respectively. Further to this systemic hypertension was the third most prevalent (12.8%) and an unknown etiology of CKD was reported in 21.8% of the total participants. These results were similar to those of the study by Magdy et al, which showed that patients with CKD had a high prevalence of DM (40% in the hemodialysis group and 40.9% in the group receiving conservative management), followed by hypertension in both groups at 29.24% in the HD group and 36.36% in the group receiving conservative management.[115] Mahdavi-Mazdeh et al. observed a similar finding, citing hyperglycemia as the most frequent cause of CKD.[113] With a permanent catheter in 3 patients, an AV fistula in 22 patients, and an IJV catheter in 14 patients, the length of HD was reported as a mean year of 16.03±5.76.

A significant difference was reported in both groups concerning levels of serum urea. serum creatinine, and alkaline phosphatase with a p-value <0.0001, followed by serum calcium (p-value 0.021). This study finding was similar to Madgy et al, which demonstrated a significant difference in similar laboratory parameters in participants in the HD group.[115] However, no notable variations were reported for AV access location, ECG changes, Hb, and serum

phosphorus. Overall, the laboratory parameters were significantly higher in the HD group when compared to the conservative management group. This was also reported by Havlucu et al. in 23 predialysis and 25 HD patients, in whom arterial pressure was increased due to PHT where AVF flow was positively impacted by cardiac output values and the duration of chronic renal failure, while residual urine volume was negatively impacted by arterial pressure in PHT patients.[115] Similar reports were demonstrated in the study by Elshinnawy where patients with PHT and hemodialysis had significantly higher AVF flow and correlation of mean arterial pressure with the AV flow.[114]

The HD group had a considerably greater prevalence of PHT in the current study (38.5%), due to physiological changes; higher AV flow, elevated serum creatinine, serum calcium, serum urea, and alkaline phosphatase when compared with the conservative group. The size or location of the AVF, among other things, may play a role in the mechanism that raises arterial pressure.[116] Similar to our study, Beigi et al. showed a positive association between mean fistula flow and arterial pressure; however, they also reported an inverse correlation between PAP and ejection fraction. [117]

Our study revealed that most of the patients undergoing hemodialysis are presented with pulmonary hypertension and elevated laboratory markets which is also reported by previous studies.

CONCLUSION

CONCLUSION:

Pulmonary hypertension was found to be more prevalent among CKD patients on Hemodialysis compared to CKD patients on conservative management. PH can be used as an indicator for assessing severity of the disease using echocardiogram.

SUMMARY

SUMMARY:

The present cross-sectional study was conducted among CKD patients at R.L Jalappa Hospital and Research Centre,Tamaka, Kolar during period of January 2021 to May 2022. Writtten informed consent was obtained, Patients were randomly divided into two groups. Group A: CKD patients on Hemodialysis and Group B: CKD patients on Conservative management. Echocardiography and blood investigations were done. Collected data were coded and entered into an excel data base. All the data were analysed using SPSS v22 operating on windows 10 with a $p<0.05$ considered statistically significant.

The current study was conducted among 78 patients with a high prevalence of CKD in the age group between 51-60 years of age (46.2%) and male predominance (56.4%). Diabetes mellitus was reported to be the most common etiology (24.4%), followed by diabetes and hypertension together (24.4%), and CKD of unknown etiology (21.8%).

The study showed that both CKD patients receiving dialysis and those not receiving it had a significant incidence of pulmonary hypertension, but those receiving hemodialysis had the highest frequency of PH (38.5%). A positive correlation was reported between the serum urea, serum creatinine, serum calcium, and alkaline phosphatase which can be associated with the development of PH in CKD patients.

Early detection of PH is an essential factor for preventing future complications, changing dialysis modality, or referring for renal transplantation. There is a need for further studies to evaluate the outcome of patients with CKD and hemodialysis and evaluate the need for renal replacement. In addition, laboratory markers such as serum urea, creatinine, phosphorus, and alkaline phosphatase can be used to assess the development of PH in CKD .

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ANNEXURES

ANNEXURE – I

PROFORMA

Name:

Age:

Sex:

Occupation:

UHID number:

Phone number:

Address:

Complaints with duration:

Previous history:

Family history:

Past history:

GENERAL PHYSICAL EXAMINATION:

Built and nourishment:

Pallor/Cyanosis/Icterus/Clubbing/edema/Generalized lymphadenopathy

VITAL DATA:

Pulse:

Temperature:

BP:

Respiration rate:

Systemic examination:

Per abdomen:

Respiratory system:

Cardio vascular system:

Central nervous system:

INVESTIGATIONS

COMPLETE HEMOGRAM

BLOOD UREA

SERUM CREATININE

SERUM ELECTROLYTES

SPECIFIC PARAMETER

ECG

ECHOCARDIOGRAM

eGFR using MRMD EQUATION

ANNEXURE – II

INFORMED CONSENT FORM

I Mr./Mrs. _____ have been explained in my own understandable language, that I will be included in a study which is **"A COMPARATIVE STUDY OF PULMONARY HYPERTENSION AMONG CHRONIC KIDNEY DISEASE (CKD) PATIENTS ON DIALYSIS AND ON CONSERVATIVE LINE OF TREATMENT".**

I have been explained that my clinical findings,investigations,treatment and prognosis will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary and I can withdraw from the study any time and this will not affect my relation with my doctor or treatment for my ailment.

I have been explained about the risk/benefit of the study.

I understand that the medical information produced by this study will become part of institutional records and will be kept confidential by my said institute.

I agree not to restrict the use of any data or result that arise from this study provided such a use is only for scientific purpose(s).

I have principal investigator mobile number for enquiries.

I have been informed that standard of care will be maintained throughout the treatment period.

I in my sound mind give full consent to be added in the part of this study.

Investigator: Dr. INBA PRAVEEN I
Phone number : 9788855754

Participant's signature/ thumb impression

Name:

Signature/thumb impression of the witness: Date:

Name:
Relation to patient

ANNEXURE – III

PATIENT INFORMATION SHEET

STUDY TITLE: "A COMPARATIVE STUDY OF PULMONARY HYPERTENSION AMONG CHRONIC KIDNEY DISEASE (CKD) PATIENTS ON DIALYSIS AND ON CONSERVATIVE LINE OF TREATMENT"

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

AIMS OF THE STUDY:

To determine and compare the proportion of Pulmonary Hypertension among Chronic Kidney Disease patients on conservative management and on Hemodialysis.

Chronic kidney disease (CKD) encompasses a spectrum of pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR).CKD in INDIA are associated with increased morbidity and mortality, decreased quality of life and increased healthcare expenditures,at Sri Devaraj Urs Academy of Higher Education & Research has decided to undertake a study on this regard.

We are inviting the patients with CKD to take part in this study, however based on criteria list, eligible participants will be chosen among the interested ones.

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. If you agree to participate in this study, you will undergo echocardiogram. We will collect blood samples to test CBC & eGFR using MRMD & also assess your balance. You can take your regular antidiabetic and hypertensive medications during the exercise sessions.

By participating in this research you will benefit by improved strength, balance required to do your daily activities effectively. Your participation will also help us to use the outcomes of this study for future subjects. Your participation in this study will not put you at any risk.

All information collected from you will be strictly confidential & will not be disclosed to any outsider. This information collected will be used for research purpose. This information will not reveal your identity & this study have been reviewed by central ethical committee.

There is no compulsion to participate in this study, further you are at the liberty to withdraw from the study at any time if you wish to do so. Your treatment aspect will not be affected if you not wish to participate. You are required to sign only if you voluntarily agree to participate in proposed study. A copy of this document will be given to you for your information.

MASTER CHART