IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 18, Issue 6 Ser. 1 (Nov. – Dec. 2023), PP 21-28
www.Iosrjournals.Org

A Study Of Pulmonary Hypertension In Hemodialysis Patients- Its Epidemiology, Risk Factors, And Association With Cardiovascular Morbidity

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Abstract:
Background: *Pulmonary hypertension (PH) is a multifaceted and incapacitating medical illness distinguished by elevated blood pressure in the pulmonary arteries. The occurrence of a certain complication in patients with chronic kidney disease (CKD) has lately gained recognition. This complication has been identified as an independent predictor of higher mortality rates in individuals undergoing dialysis or kidney transplantation. Nevertheless, there is a lack of epidemiological data regarding the prevalence of Pulmonary Hypertension in individuals with End-Stage Renal Disease (ESRD) or early stages of Chronic Kidney Disease (CKD), as well as its potential link with cardiovascular morbidity. This scarcity of information extends to India, and specifically, no previous studies have been identified in the region of Rajasthan. Based on the aforementioned context, a research study was designed with the objective of determining the prevalence of pulmonary hypertension and its correlation with cardiovascular morbidity in individuals with chronic kidney disease (CKD).*
Material & Methods*: Study was undertaken in the Nephrology Department of NIMS Hospital in Jaipur, spanning from January 1, 2021, to January 1, 2023. The study population consisted of patients diagnosed with stage-V chronic kidney disease (CKD) who were undergoing maintenance hemodialysis. A logistic regression model was employed to assess the correlation between pulmonary hypertension and cardiac morbidity.*
Results: *Pulmonary hypertension was seen in 334 individuals, accounting for 47.4% of the study population. The mean systolic pulmonary artery pressure (SPAP) among these patients was 7.4+/-11.4 mmHg, with a range of 35 to 92 mmHg. The incidence of pulmonary hypertension (PH) in chronic kidney disease (CKD) stages 1-5 was found to be 14.3% (12 out of 84), 33.3% (21 out of 63), 38.9% (42 out of 108), 40.9% (54 out of 132), and 64.5% (205 out of 318).The study found that there was a significant correlation between the severity of pulmonary hypertension (PH) and the risk of cardiac morbidity. The odds ratios (with corresponding 95% confidence intervals) for mild PH, moderate PH, and severe PH were 1.79 (1.30–2.47), 2.75 (1.73–4.37), and 3.90 (1.46–10.42), respectively.*
Conclusion: *The present study aimed to examine the impact of pulmonary hypertension on individuals undergoing hemodialysis, while also assessing the associated risk of cardiovascular morbidity. The occurrence of mild-to-moderate pulmonary hypertension (PH) is more prevalent in individuals with advanced chronic kidney disease (CKD), but severe PH is infrequently observed in individuals with CKD who do not have end-stage renal disease (ESRD).*

Keywords: *cardiovascular (CV) morbidity, chronic kidney disease (CKD), End stage renal disease (ESRD), pulmonary hypertension (PH).*

Date of Submission: 24-10-2023 Date of Acceptance: 04-11-2023

I. BACKGROUND:

Pulmonary hypertension (PH) is a multifaceted and incapacitating medical illness defined by elevated blood pressure in the pulmonary arteries. Pulmonary hypertension (PH) has emerged as a prevalent consequence of chronic kidney disease (CKD) it has been identified as an autonomous prognostic factor for heightened mortality in individuals undergoing dialysis and kidney transplantation. The characteristic feature of this life-threatening disorder is an increased pulmonary artery pressure (PAP), which has been recognized as a newly discovered risk factor and a notable component in individuals suffering from end-stage renal diseases. [1–4]. Based on an echocardiographic diagnosis of PH, the prevalence of PH in people with Stage 5 chronic kidney disease (CKD) ranges from 9% to 39%; in people receiving hemodialysis, it ranges from 18.8% to 68.8%; and in people receiving peritoneal dialysis, it ranges from 0% to 42%. [5-8]

The exact etiology of pulmonary hypertension (PH) within this particular cohort remains incompletely understood. The presence of left ventricular dysfunctions and risk factors associated with chronic kidney disease (CKD), including volume overload, arteriovenous fistulas, sleep apnea, exposure to dialysis membranes, endothelial dysfunction, vascular calcification and stiffness, and severe anemia, have the potential to induce or exacerbate pulmonary hypertension (PH). The user has provided a numerical sequence [2,3]. In 2008, the World Symposium of Pulmonary Hypertension (WSPH) held in Dana Point introduced a classification system that included end-stage renal disease (ESRD)-related pulmonary hypertension (PH) as the fifth subtype of PH, specifically categorized as PH with multifactorial reasons of unknown origin. The information was subsequently revised in a publication by Nice in 2013. According to reference [10]. The impact of PH on patients with end-stage renal disease (ESRD) remains uncertain. The precise mechanisms and developmental stage at which pulmonary hypertension (PH) originates remain elusive. The timely identification and intervention of pulmonary hypertension (PH) may result in improved long-term outcomes. [11].
There are a number of risk factors that have a direct impact on pulmonary hypertension in hemodialysis patients.

The following are risk factors;

1. High Cardiovascular Risk: "Hemodialysis" patients already have a high burden of cardiovascular risk factors, which can aid in the development of PH (Lasa, *et al.,* 2020). These risk factors include hypertension, diabetes, dyslipidemia, and smoking.

2. Fluid Overload Hemodialysis patients frequently develop fluid overload because their ability to remove fluid during treatments is limited. Over time, this fluid overflow may cause lung pressures to rise.

3. Chronic Inflammation: Chronic inflammation, which is linked to the emergence of PH, is a common condition in hemodialysis patients (Levine, 2021). Increased pulmonary pressures can result from endothelial dysfunction and remodeling of the pulmonary arteries, both of which are brought on by inflammation.

4. Vascular Calcification: A frequent complication in hemodialysis patients, vascular calcification can compromise the pulmonary arteries and aid in the onset of PH.

In order to prevent CKD patients from developing ESRD, it is essential to look into the epidemiology of PH. Epidemiological information on Pulmonary Hypertension (PH) in ESRD or earlier stages of CKD and its association with cardiovascular (CV) morbidity, particularly India, is still lacking. It is also uncertain whether PH and CV disease exist in other stages of CKD. Despite its prognostic importance, it is unknown how common PH is in CKD. The pathogenesis of PH in CKD is also poorly understood. In light of this, a study was designed to determine the prevalence of pulmonary hypertension and its relationship to cardiovascular morbidity in CKD patients.

II. MATERIAL & METHODS:

This prospective study was conducted in Nephrology Department, NIMS Hospital, Jaipur between January 1, 2021, to January 1, 2023, and all adult patients with CKD stage-V on maintenance hemodialysis were screened for eligibility of inclusion.

Inclusion criteria:

Participants included individuals who were ≥18 years of age and had been diagnosed with chronic kidney disease. These individuals were receiving continuous hemodialysis treatment for a minimum of three months. Additionally, complete clinical and echocardiographic records were obtained for each participant.

Exclusion criteria:

This study excludes individuals who fall into the following categories: patients undergoing maintenance peritoneal dialysis, patients who have been on hemodialysis for less than three months, patients with pulmonary hypertension resulting from chronic obstructive pulmonary disease (COPD) or collagen vascular disease, patients with a history of pulmonary embolism or conditions affecting the chest wall or lung tissue, patients with rheumatic heart disease (RHD), patients with congenital heart disease (CHD), patients with acute heart failure (AHF), and patients with portal hypertension.

Data Collection & Analysis:

The, echocardiography, clinical data and laboratory investigations findings of the study individuals were organized and compiled in a pre-designed performa as follows.

A. The documentation of clinical records and the conduct of laboratory investigations are essential components of the medical field. Data pertaining to demographic characteristics such as age and gender, as well as physiological measurements including systolic blood pressure (SBP), body mass index (BMI), diastolic blood pressure (DBP) and the underlying cause of chronic kidney disease (CKD), along with relevant medical history such as smoking habits, hypertension, diabetes and coronary heart disease (including a history of coronary artery

bypass grafting or percutaneous coronary intervention), as well as other cardiovascular comorbidities, have been documented. Additionally, laboratory parameters have been recorded. The laboratory measures that were included in the study were serum albumin, Hemoglobin, serum uric acid, serum phosphorus, serum calcium, random blood sugar (RBS), intact parathyroid hormone (iPTH) and fasting lipid profile.

B. Echocardiographic findings:

1) Pulmonary Hypertension (PH) detection by echocardiography-

The echocardiographic data for each participant in the study was collected from the Magnetic Resonance Imaging and Echocardiography laboratory located within the hospital. In the analysis, only the initial hospitalization during the study period was taken into account for individuals with repeated hospitalizations and echocardiographic data. M-mode, two-dimensional (2-D), and tissue Doppler echocardiography were conducted on all participants utilizing an echocardiographic imaging equipment that was equipped with a transducer operating at a frequency range of 2.0–3.5 MHz. The assessment and computation of systolic pulmonary artery pressure (SPAP) is conducted by the utilization of a modified Bernoulli equation. [12].

Interpretation: A number equal to or more than 35 mmHg has been characterized as pulmonary hypertension (PH). The categorization of the severity of Pulmonary Hypertension (PH) has been based on the systolic pulmonary artery pressure (SPAP) and is as follows: [13]

- Mild: 35–50 mmHg
- Moderate: 50–70 mmHg
- Severe: > 70 mmHg

(2) Additional findings of echocardiographic:

a) Regurgitation valvular disease: The condition of regurgitation valvular disease is characterized by the presence of moderate to severe regurgitation in either the mitral valve, the aortic valve, or both. This classification is established according to the guidelines provided by the European Association of Echocardiography for the evaluation of valvular regurgitation.

b) Pericardial effusion: The degree of pericardial effusion can be classified as trace to tiny when the pericardial gap is separated by less than 1 cm in diastole, regardless of the plane of measurement.

Moderate or severe effusion is characterized by a pericardial space separation of greater than 1 cm during diastole, as previously stated.

c) The determination of left ventricular systolic and diastolic dysfunction is based on the criteria outlined in the 2012 guidelines issued by the European Society of Cardiology (ESC) for the assessment of acute and chronic heart failure, in conjunction with recommendations from the European Association of Echocardiography and American Society of Echocardiography.[14]

The assessment of cardiovascular morbidity:

The assessment of cardiovascular morbidity is conducted based on data obtained from the hospital's Medical Records Database (MRD). This database encompasses various cardiac conditions such as acute heart failure (AHF), angina, acute myocardial infarction, sudden death, and arrhythmias necessitating hospitalization. Additionally, it includes cerebrovascular diseases such as peripheral vascular diseases, transient ischemic attack and thromboembolic or hemorrhagic stroke.[15].

Acute heart failure (AHF) is characterized as either the emergence of heart failure (HF) for the first time or the deterioration of chronic HF, resulting in symptoms severe enough to require hospitalization. The diagnosis of acute heart failure (AHF) relies on the criteria established by the European Society of Cardiology.

Statistical Analysis:

The data was inputted into Microsoft Excel and subsequently analyzed using SPSS Version 23. The categorical data was summarized by representing it with numerical values and percentages. To determine the statistical significance of differences, the chi-square (χ^2) test was employed. The continuous variables were summarized by use either medians and interquartile ranges or means and standard deviations. The study employed Student's t-test to evaluate differences between groups for variables that exhibited a normal distribution. Conversely, the Wilcoxon rank sum test was utilized to analyze differences for variables that did not follow a normal distribution. The stepwise forward logistic regression analysis was employed to assess the clinical factors linked to pulmonary hypertension (PH) or cardiovascular (CV) morbidity. Statistical significance was determined for the observed differences at a two-sided P-value of less than 0.05. A logistic regression model was employed to assess the correlation between pulmonary hypertension and cardiac morbidity.

III. RESULTS:

A total of 705 patients were screened over the study period in accordance with the predetermined inclusion and exclusion criteria. There were 317 individuals identified as females, while 388 individuals were identified as males. The average age was 52.5 years with a standard deviation of 18.0 years. Pulmonary hypertension was seen in 334 individuals, accounting for 47.4% of the patient population. The mean systolic pulmonary artery pressure (SPAP) was found to be 7.4+/-11.4 mmHg, with a range spanning from 35 to 92 mmHg. The prevalence rates of mild, moderate, and severe pulmonary hypertension (PH) were determined to be 22.1%, 15.04%, and 10.2% among the patient population, respectively. [Fig.1]

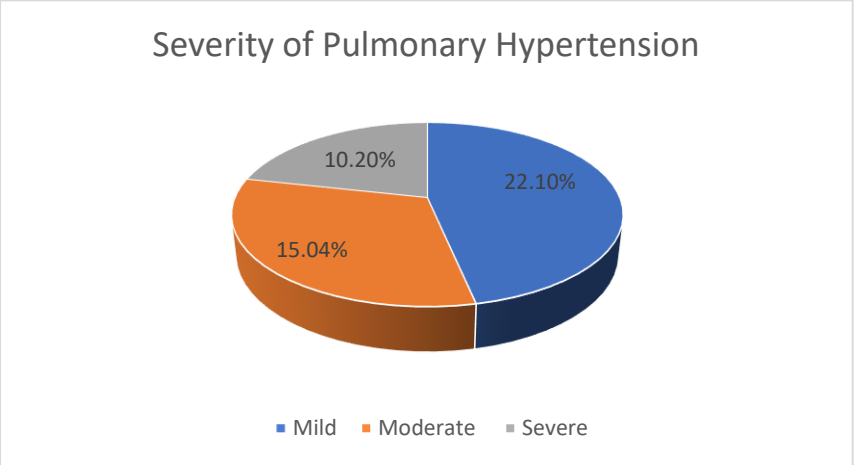

Figure 1: Percentage of study subjects by severity of Pulmonary Hypertension

The incidence of pulmonary hypertension (PH) in patients with chronic kidney disease (CKD) stages 1-5 was found to be 14.3% (12 out of 84 patients), 33.3% (21 out of 63 patients), 38.9% (42 out of 108 patients), 40.9% (54 out of 132 patients), and 64.5% (205 out of 318 patients) as illustrated in Figure 2. Severe pulmonary hypertension (PH) was identified in patients with chronic kidney disease (CKD) at Stages 5 and 5D.

Out of the total population of patients diagnosed with Chronic Kidney Disease (CKD), a subset comprising 331 individuals has undergone dialysis treatment. In contrast to non-dialysis patients, the incidence of pulmonary hypertension (PH) was significantly greater among individuals who underwent dialysis. Frequent occurrences of mild-to-moderate pulmonary hypertension (PH) were observed in patients undergoing dialysis. Nevertheless, no significant disparity was observed in the prevalence of severe pulmonary hypertension (PH) among individuals undergoing dialysis compared to those not undergoing dialysis

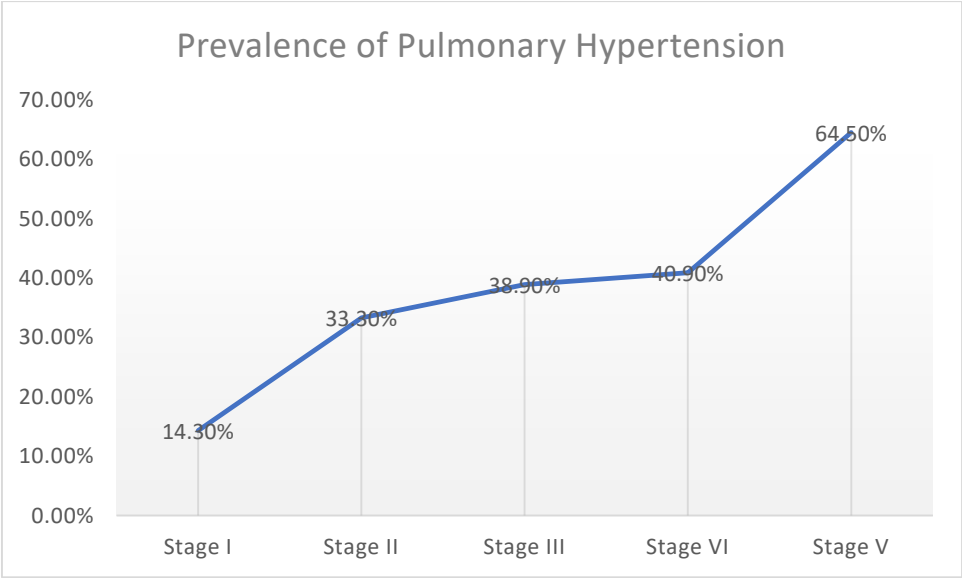

Figure 2: Prevalence of Pulmonary Hypertension in CKD Stages

The factors influencing the pH levels in people with chronic kidney disease (CKD):

Table 1 presents the laboratory, hemodynamic, demographic, and clinical, parameters of the study population categorized according to the severity of pulmonary hypertension.

Table 1. Clinical parameters and Baseline demographic of different CKD stages

No. of patients	CKD1	CKD2	CKD3	CKD4	CKD5	All
Age (years)	34.5+/-15.6	46.8+/-17.8	54.9+/-17.1	51.6+/-16.7	55.4+/-17.5	52.5+/-18.0
Gender (Female/male)						317/388
Systolic BP	128+/-20	140+/-24	148+/-26	145+/-24	154+/-26	149+/-27
Diastolic BP	78+/-13	84+/-15	84+/-17	84+/-14	85+/-15	83+/-16
BMI	22.1+/-3.9	22.7+/-3.2	23.0+/-3.0	23.3+/-3.4	22.2+/-3.1	22.3+/-5.4
eGFR (ml/min/1.73 m2, CKD-EPI)	116.6+/-18.1	75.1+/-8.4	52.1+/-4.8	37.6+/-4.1	21.6+/-4.3	11.2(5.3–51.7)
With Diabetes	9.4 %	17.9%	27.5%	35.5%	34.3%	27.7%
With Hypertension	33.5%	58.3%	78.3%	80.1%	87.8 %	76.6%

** LDL: low density lipoprotein BP: blood pressure; CAD: coronary artery disease; eGFR: evaluated glomerular filtration rate; LV: left ventricular, LVEF: left ventricular ejection fraction; CV: cardiovascular; PH: pulmonary hypertenstion, HDL: high density lipoprotein, moderate to severe regurgitation valvular disease; CKD: chronic kidney disease; NA: not available; Data are given as mean, median, standard deviation*

Table 2. Laboratory parameters of different CKD stages

No. of patients	CKD1	CKD2	CKD3	CKD4	CKD5	All
Proteinuria (g/24 h)	1.7(0.6–4.4)	2.0(0.7–4.6)	1.8(0.5–4.6)	2.4(0.6–5.3)	2.5(0.8–4.2)	2.0(0.8–4.0)
Hemoglobin (g/L)	129+/-21	127+/-24	124+/-24	114+/-23	102+/-24	103+/-28
Albumin (g/L)	24.5+/-10.7	28.9+/-10.1	26.4+/-10.0	26.5+/-9.5	26.6+/-8.2	27.3+/-7.8
Uric acid (mmol/L)	366+/-106	413+/-116	433+/-116	466+/-119	474+/-146	433+/-134
Cholesterol (mmo/L)	7.1+/-3.4	6.5+/-3.1	6.4+/-3.0	6.0+/-2.6	5.7+/-2.7	5.4+/-2.5
Triglycerol (mmo/L)	2.2+/-1.7	2.1+/-1.8	1.9+/-1.2	2.2+/-2.0	1.9+/-1.5	1.8+/-1.5
HDL-cholesterol (mmol/L)	1.3+/-0.5	1.3+/-0.5	1.2+/-0.4	1.2+/-0.5	1.1+/-0.4	1.2+/-0.4
LDL- cholesterol (mmol/L)	4.0+/-2.3	3.5+/-2.0	3.6+/-1.8	3.2+/-1.7	3.0+/-1.5	2.9+/-1.6

In comparison to individuals without pulmonary hypertension (PH), patients who have been diagnosed with PH demonstrate reduced levels of albumin, hemoglobin, complement 3, estimated glomerular filtration rate (eGFR), and left ventricular ejection fraction (LVEF). In contrast, the patients with pulmonary hypertension (PH) had increased levels of parathyroid hormone (PTH), proteinuria, body mass index (BMI), triglyceride (TG) and length of dialysis blood pressure (both systolic and diastolic). In the context of examining the frequency of pulmonary hypertension (PH) in individuals with chronic kidney disease (CKD), several variables were identified as independent risk factors. These variables include proteinuria, hemoglobin levels, triglyceride levels (TG), body mass index (BMI), estimated glomerular filtration rate (eGFR), parathyroid hormone (PTH) levels. The covariates were treated as variables, while the dependent variable was deemed to be PH. The main causes of chronic kidney disease (CKD) include diabetic nephropathy, hypertension nephrosclerosis (19.2%), chronic glomerular diseases (42.3%).

Epidemiology of PH and CV morbidity in different stages of CKD:

The study findings indicated that 50.5% of patients diagnosed with pulmonary hypertension (PH) had pericardial effusion. Additionally, 64.1% of these patients displayed moderate-to-severe mitral and/or aortal regurgitation, while 16.9% exhibited left ventricular systolic dysfunction. Furthermore, 46.2% of patients demonstrated diastolic dysfunction, and 48.4% experienced cardiovascular morbidity. A total of 194 individuals (27.5%) exhibited cardiovascular morbidity. The prevalence of cardiovascular morbidity in individuals with chronic kidney disease stages 1-5D was found to be 4.3%, 14.2%, 20.3%, 26.1%, 28.1%, and 50.9%, respectively. (Figure 3).

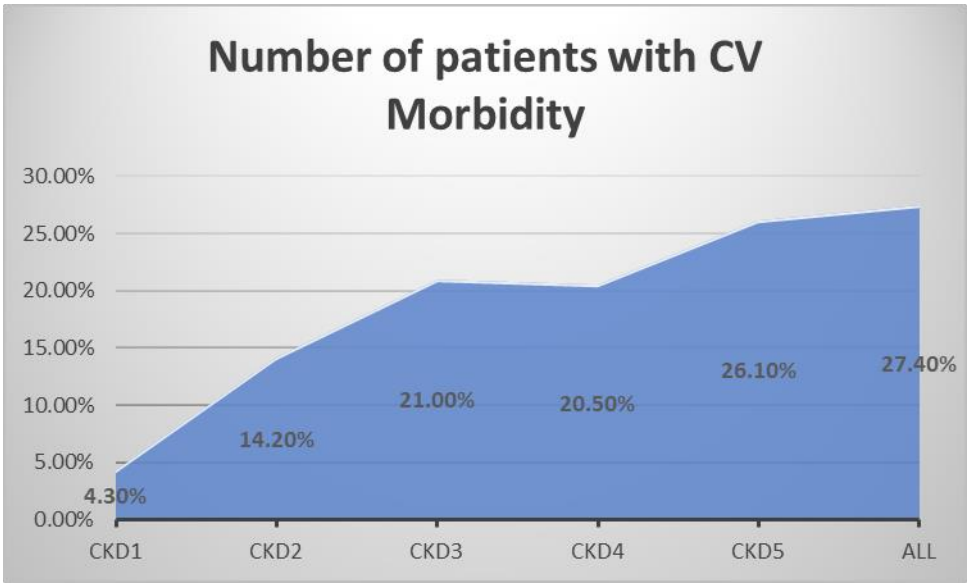

Figure 3: Distribution of patients with CV morbidity

The present study investigates the potential association between cardiac morbidity and pulmonary hypertension (PH) in patients with chronic kidney disease (CKD):

The analysis focused on assessing the relationship between the severity of pulmonary hypertension (PH) and the risk of cardiac morbidity. A binary logistic regression analysis was conducted to examine the relationship between cardiac illnesses and pulmonary hypertension (PH) in patients with chronic kidney disease (CKD), utilizing variables that had a significance level of $p<0.1$. The likelihood of experiencing cardiac morbidity was shown to be higher as the grade of pulmonary hypertension (PH) rose. The adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated to be 1.79 (1.30–2.47) for mild PH, 2.75 (1.73–4.37) for moderate PH, and 3.90 (1.46–10.42) for severe PH ($p<0.001$). Following the adjustment, there was no discernible change in the risk of chronic kidney disease (CKD) across stages 1 to 4. Nevertheless, the incidence of cardiovascular morbidity escalated upon the onset of end-stage renal disease (ESRD).

IV. DISCUSSION:

Pulmonary hypertension (PH) is a complex disease distinguished by increased blood pressure in the pulmonary arteries, which progressively damages the heart and lungs. PH is a severe side effect that affects hemodialysis patients and raises cardiovascular morbidity and death. [16]

According to various scholarly evaluations, the majority of PH varied from 0 to 42% in those getting peritoneal dialysis, 18.8 to 68.8% in those receiving hemodialysis, and 9 to 39% in those with stage 5 CKD. For CKD in its early stages, there aren't much epidemiologic data available.

The research will not find any gender-specific risk for PH in renal disease. Here, data from observational research may be used to pinpoint factors that influence the development of PH, along with it will provide new "potential therapeutic targets for clinical trials". Patients with a prevail vasculopathy might be simpler to decide on the treatment with vasodilator treatments like phosphodiesterase inhibitors, endothelin receptor bad guys, or prostanoid analogs that have been displayed to further develop practice resilience and lessen pneumonic vascular obstruction in non-uremic "PAH patient" (de Perrot et al., 2021). [17]

Different investigations have demonstrated that PH repeatedly affected people with "chronic kidney disease (CKD)", particularly those with "end-stage renal disease (ESRD)". To explore the prevalence of PH before stage 5 of CKD, however, there aren't much epidemiologic data available. In this study, patients with CKD at different stages, including those with HD and PD, were found to have a higher prevalence of PH; the link between PH and CKD was also looked at. In this study, the prevalence of PH ranged from 0 to 42% in those getting peritoneal dialysis, 18.8 to 68.8% in those receiving hemodialysis, and 9 to 39% in those with stage 5 CKD. (Chang, *et al.*, 2022). [18]

According to this assignment, around 37.5% of people with CKD Stages 1 through 5D have PH. In this study, the overall prevalence of PH in the CKD group was 47.38%. For more than 10 years, prostacyclin has served for PH treatment. Additionally, it appears to have ant proliferative and cytoprotective properties that were employed to treat CKD. So, in CKD stages 3-5, the distribution of mild, moderate, and severe PH may be affected by prostacyclin. Doppler-estimated PASP levels were noticeably higher in dialysis patients. People with HD and PD have an overall prevalence of PH. However, moderate-to-severe PH was distributed differently in

dialysis patients. It should be highlighted that despite their potential, a number of factors in the current investigation were not independent predictors of PH. A progressive condition, CKD involves a variety of etiologies, including polycystic kidney disease, lupus nephritis, diabetic nephropathy, and glomerulonephritis, some of which are linked to the prevalence of PH. Hypertension causes left ventricular diastolic dysfunction, a change that will inevitably raise pulmonary venous and arterial pressure

Based on the observed result from the primary analysis, it can be expressed that CKD/ESRD population, PH has thus far gone untreated as a co-morbidity. Since a strong correlation between the existence of PH in "CKD" and increased hospitalization and mortality was discovered, it has recently become a focus of research. Kidney function, particularly left ventricular systolic and diastolic dysfunction, is a frequent co-morbidity and an independent risk factor for poor outcomes in a variety of cardiovascular illnesses.[19]

By worsening pulmonary vasculature and cardiac remodeling, impaired kidney function can speed up the course of PH. Therefore, it should be clear why early detection of PH in a patient with CKD is important since it enables targeted therapy that may have a "reno-protective" impact and lower cardiovascular morbidity.

Evaluation of Cardiovascular morbidity

Patients on hemodialysis who have pulmonary hypertension had higher cardiovascular morbidity and mortality. Here, in this study CV morbidity has been used as per the evidence from the MRD database of the hospital which incorporated with angina, acute myocardial infarction, sudden death, and arrhythmias necessitating hospitalization are examples of cardiac, cerebral (TIA, thromboembolic or hemorrhagic stroke), and peripheral vascular disorders. The study critically evaluated that several factors like heart failure left ventricular hypertrophy, and right ventricular dysfunction all advance as a result of. In hemodialysis patients, the presence of PH is a standalone predictor of mortality. [20]

V. CONCLUSION:

This study investigated the effect of pulmonary hypertension in hemodialysis patients along with the measurement of the risk of cardiovascular morbidity. The occurrence of mild-to-moderate pulmonary hypertension (PH) is more common in individuals with advanced chronic kidney disease (CKD), but severe PH is rare in individuals with CKD who do not have end-stage renal disease (ESRD). The presence of pulmonary hypertension (PH) in chronic kidney disease (CKD) has been found to be linked to cardiac illness, but not cerebrovascular disease. Furthermore, it has been observed that as the severity of PH increases, there is a corresponding increase in cardiac morbidity.

On a concluding note, it can be stated that occurrence of pulmonary hypertension is high with the weakening of kidney operation. Thus it can be mentioned that hemodialysis patients have a high prevalence range of PH. Traditional risk factors, variables associated with dialysis, anemia, CKD-MBD components, and inflammation or oxidative stress did not have an impact on the occurrence of PH in the HD group. Both left and right systolic dysfunction is present in HD patients with PH, and they also frequently have mitral regurgitation which is well presented in this study.

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