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Prevalence of pulmonary hypertension in chronic kidney disease patients attending a tertiary care center hospital

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Abstract

Pulmonary hypertension is associated with poor outcomes in chronic kidney disease and general populations, it causes increased risk of cardiovascular events and death. Identifying pulmonary hypertension in this population is challenging but is important in this population since management strategies differ from those for patients with chronic kidney disease who do not have pulmonary hypertension. There are only limited date regarding the association between pulmonary hypertension and chronic kidney disease. In this cross sectional study the primary objective of the study was to estimate the prevalence of pulmonary hypertension in stage 3, 4, 5 of KDGIO classification of chronic kidney disease patients attending medicine department of MCH Ernakulam. Secondary Objective was to find out the association between variables like age, gender, anemia, left ventricular ejection fraction, dialysis dependent chronic kidney disease, stage of chronic kidney disease, in the development of pulmonary hypertension in chronic kidney disease patients. In this cross-sectional study, 150 patients belonging to chronic kidney disease stage 3,4, and 5 more than 18 years of were included in this study. Routine blood examination done and

classified patients into chronic kidney disease stages. Ejection fraction and tricuspid regurgitant flow velocity is estimated using echocardiogram. Tricuspid regurgitation velocity more than 3.4 m/s is considered as pulmonary hypertension. Then each variable is compared univariably for its association with pulmonary hypertension. From our study it was obtained that the prevalence of pulmonary hypertension in chronic kidney disease stage 5 patients was significantly high. Prevalence of pulmonary hypertension was significantly high among dialysis patients. In these patients, mean haemoglobin concentration among those with pulmonary hypertension is less compared to those without pulmonary hypertension. There was no significant correlation between pulmonary hypertension in chronic kidney disease and age or gender

Prevalence of pulmonary hypertension in chronic kidney disease will help as to formulate measures for its prevention and treatment strategies in this population thus increasing life expectancy in them

Keywords: Chronic Kidney Disease, Pulmonary Hypertension

Introduction

Chronic kidney disease encompasses a spectrum of pathophysiologic processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate, it is associated with increased risk of ESRD, cardiovascular events, and mortality. There has been an increasing interest in studying the association between pulmonary hypertension and chronic kidney disease, which itself is a risk factor for morbidity and mortality. Pulmonary hypertension is defined as resting mean pulmonary arterial pressure >25 mm hg which is measured via right heart catheterization. Although the exact mechanism that underlying the presence of pulmonary hypertension in chronic kidney disease are mostly unknown, factors related to decreased GFR and the management of kidney failure have been implicated. Chronic volume overload may accelerate pulmonary vascular remodeling in subgroups of patients with chronic kidney disease. Nitric oxide signaling regulates pulmonary vascular tone and is a common target for drug therapies for patients with pulmonary hypertension, multiple mediators of nitric oxide metabolism are adversely affected by chronic kidney disease. Chronic kidney disease and hemodialysis also promotes inflammation, various inflammatory markers are associated with pulmonary hypertension like TGF beta, IL6. Most patients with chronic kidney disease are affected by one or more comorbid conditions that by themselves may induce or exacerbate pulmonary hypertension. Left ventricular dysfunction associated with chronic kidney disease itself may cause pulmonary hypertension, preexisting connective tissue disorders and superimposed infections, hematologic and liver disease may contribute to pulmonary hypertension in patients with chronic kidney disease by mechanisms that interfere with microvascular tone in the lung. However collectively these factor fails to explain the prevalence of pulmonary hypertension in chronic kidney disease patients because most patients exhibit pulmonary hypertension even in the absence of these diseases.

Method of choice for diagnosis of pulmonary hypertension is right -heart catheterization, due to its invasive nature transthoracic doppler echo-cardiography can be used as a noninvasive method, here mean pulmonary arterial pressure mPAP ≥ 40mmhg is considered severe pulmonary hypertension. Variables like older age, gender, anemia, left ventricular ejection fraction, dialysis dependent and non-dialysis dependence

are studied separately and presence of any association between them and pulmonary hypertension severity in chronic kidney disease patients are assessed, this variable may increase the risk of pulmonary hypertension in chronic kidney disease. Interventions to lower cardiovascular risk in in chronic kidney disease by targeting the traditional cardiovascular risk factors have been only modestly successful at best. Therefore, there is an urgent need to evaluate novel risk factors for cardiovascular disease and mortality in chronic kidney disease that may eventually serve as therapeutic targets. Careful attention to optimizing body fluid volume in patients with chronic kidney disease by diuretics, reducing dietary salt intake, appropriate dialysis treatment intensification may reduce the burden of pulmonary hypertension, since pulmonary hypertension increase the mortality and morbidity in chronic kidney disease patients identifying and treatment of the same may increase the survival in these patients.

Materials and methods

Study design

Cross sectional study

Inclusion criteria

All consecutive CKD patients with stage 3,4 and 5 of KDGIO classification of CKD more than 18 years of age. Under treatment from government medical college Ernakulam either on conservative or maintenance hemodialysis are included in this study. Diagnosis was based on considering eGFR, renal function tests and duration of the disease.

Exclusion criteria

1. All patients with known connective tissue disease, chronic liver disease, HIV infection
2. Patients with ejection fraction <40
3. Patients with chronic lung parenchymal disease, H/o Pulmonary Tuberculosis, Pulmonary Thromboembolism, History suggestive of Obstructive sleep apnea

Sample size

According to study titled 'Prevalence, Predictors and outcomes of Pulmonary Hypertension in CKD, the prevalence of pulmonary hypertension was 21.1 %'.

By using the formula, 4PQ/d2, where P is the prevalence and absolute precision 7, the sample size was calculated to be 150

Sampling method

Consecutive cases of patients satisfying inclusion criteria were included in the study till the required sample size was met

Study variables

Age, gender, stage of CKD, left ventricular ejection fraction, anemia (Hb<12), Patients on dialysis and not on dialysis were the variables considered to be potentially correlated with PAH. These variables were considered for their association with MPAP

Data collection tools

Questionnaire (containing demographic details, clinical signs and symptoms, comorbidities, past history), Echocardiogram, Serum Creatinine, hemoglobin level

Study procedure

As per inclusion criteria CKD patients of stage 3, 4 and 5 of KDGIO classification with eGFR <60 ml/min/1.73m^2 will be selected. Thorough history and clinical examination will be done after obtaining informed consent, various tests i,e Routine Blood Examination done and classified patients into CKD stages. Ejection fraction and tricuspid regurgitant flow velocity is estimated using echocardiogram. Tricuspid regurgitation velocity more than 3.4 m/s is considered as

pulmonary hypertension. Then each variable is compared univariably for its association with PAH.

Data analysis

Data were entered in Microsoft Excel 365 Software and analysed using R software version 4.2.0.

The continuous variables like age, body weight and height, haemodynamic and haematological parameters, and biochemical parameters were summarised as mean and standard deviation. Categorical variables like gender, socioeconomic status, comorbidities, clinical features, need for dialysis, stage of CKD and prevalence of PAH were summarised as frequency and proportions. Age was also categorised into intervals of 10.

Association of PAH with continuous variables were analysed using unpaired t-test and categorical variables using Chi-square test or Fisher's exact test depending on distribution.

Ethical consideration

Institutional ethical committee clearance was obtained. All CKD patients on stage 3, 4 and 5 as per KDGIO classification who are willing to give consent were included in this study. All patients under study have full freedom to discontinue any period of time. Confidentiality was ensured

Budget

All the expenses for the investigation were met by the investigator

Observation and results

Data were entered in Microsoft Excel 365 Software and analysed using 'R' software version 4.2.0.

The continuous variables like age, body weight and height, haemodynamic and haematological parameters, and biochemical parameters were summarised as mean and standard deviation.

Categorical variables like gender, socioeconomic status, comorbidities, clinical features, need for dialysis, stage of CKD and prevalence of PAH were summarised as frequency and proportions. Age was also categorised into intervals of 10.

Association of PAH with continuous variables were analysed using unpaired t-test and categorical variables using Chi-square test or Fisher's exact test depending on distribution.

A total of 150 consecutive CKD patients were selected and the results are as follows

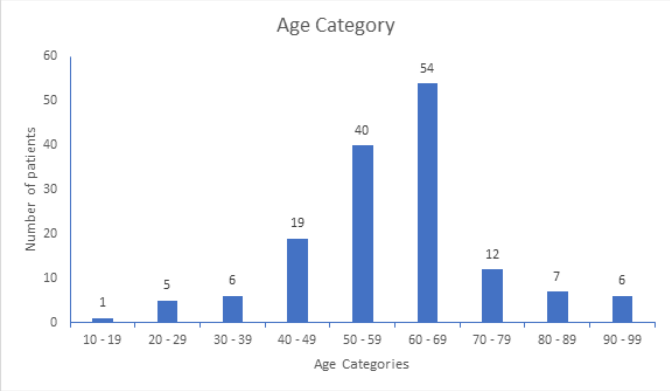


Fig. 1: Age distribution of participants

The mean age (SD) of the study participants was 60.5 (15.0) years.

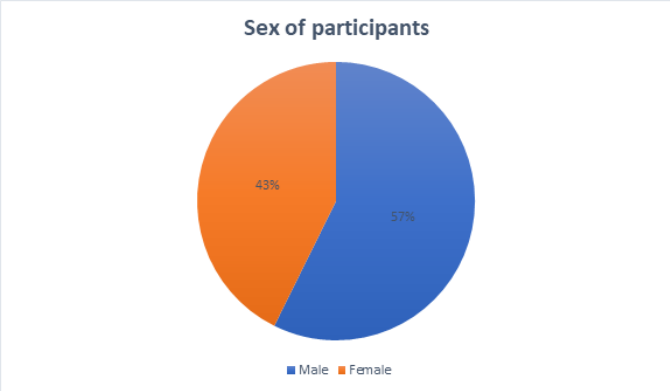


Fig. 2: Sex distribution of study participants

Out of the 150 participants, 86 (57.3%) were males.

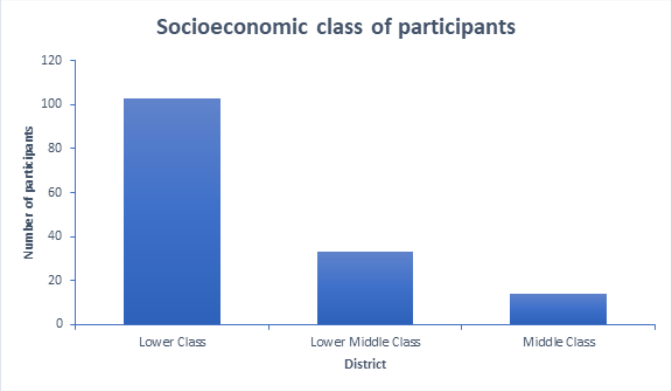


Fig. 3: Socioeconomic class of study participants

Out of the 150 participants, majority; 103 (68.7%) belonged to lower socioeconomic class.

Table 1: Comorbidities of participants

Comorbidities	N	%
CAD	42	28.0
CVA	5	3.3
Hypertension	123	82.0
Diabetes Mellitus	136	90.7
Dyslipidaemia	24	16.0

The most common comorbid condition identified among the participants was Diabetes mellitus with a prevalence of 90.7%.

Table 2: clinical features

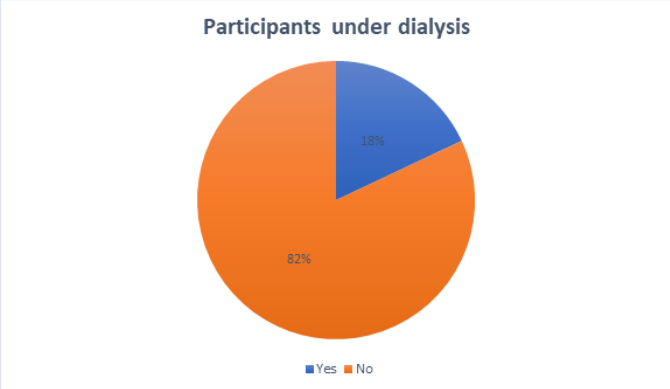
Clinical Features	N	%
Pedal Oedema	85	56.7
Anasarca	22	16.7
Reduced Urinary Output	46	30.7
Abdominal Distension	23	15.3
Breathlessness	33	22.0

The most common clinical feature present among the participants was Pedal Oedema with a prevalence of 56.7%.

Table 3: hemodynamic parameters in patients

Haemodynamic parameter	Mean	SD
Systolic Blood Pressure	133.2	13.8
Diastolic Blood Pressure	86.6	8.9
Pulse Rate	83.8	9.1
SpO_2	98.2	0.8

Fig 4: Participants under dialysis.



Of the 150 participants, 27 (18.0%) were under dialysis.

Table 4: Creatinine of the participants

	Mean	SD
Creatinine	5.6	2.3

Table 5: Stage of CKD

stage of CKD	N	%
3	5	3.3
4	44	29.3
5	101	67.3

The majority of participants were suffering from stage 5 CKD (67.3%).

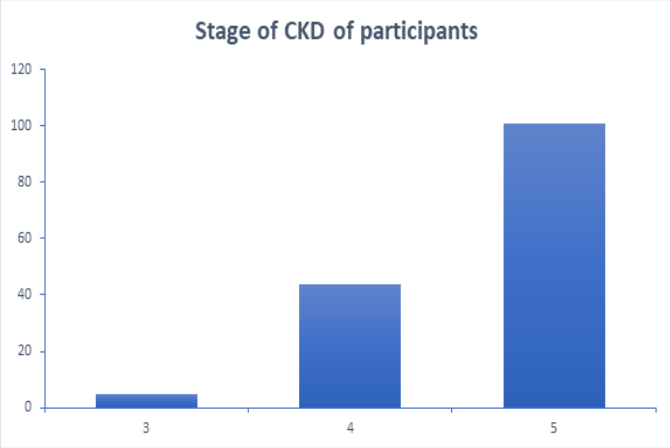


Fig. 5: Stage of CKD of study participants

Table 6: Anthropometry of study participants

Anthropometry	Mean	SD
Height	167.0	9.2
Weight	67.9	8.7
BMI	24.3	2.6

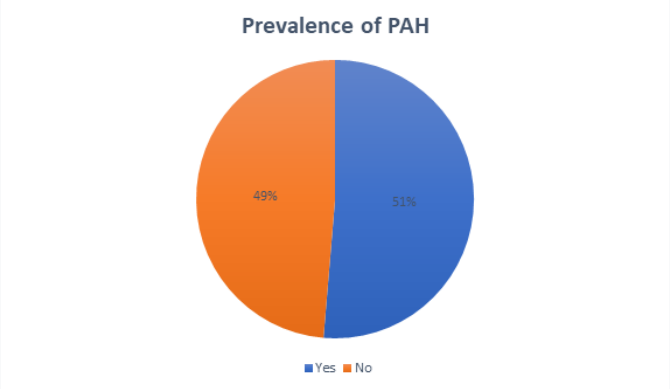
Table 7: Haemoglobin of study participants

	Mean	SD
Hb	10.1	2.3

Table 8: Ejection fraction of study participants

	Mean	SD
Ejection fraction	64.8	1.2

Fig 6: Participants with pulmonary hypertension



Of the 150 participants, 77 (51.3%, 95% CI [43.3 – 59.3]) were having PAH.

Table 9: Age of participants and presence of pulmonary hypertension

	No PAH n = 73	With PAH n = 77	p-value
Age (Mean (SD))	59.2 (11.4)	61.8 (17.8)	.29

Participants' age was not associated significantly with the presence of PAH with p-value .29.

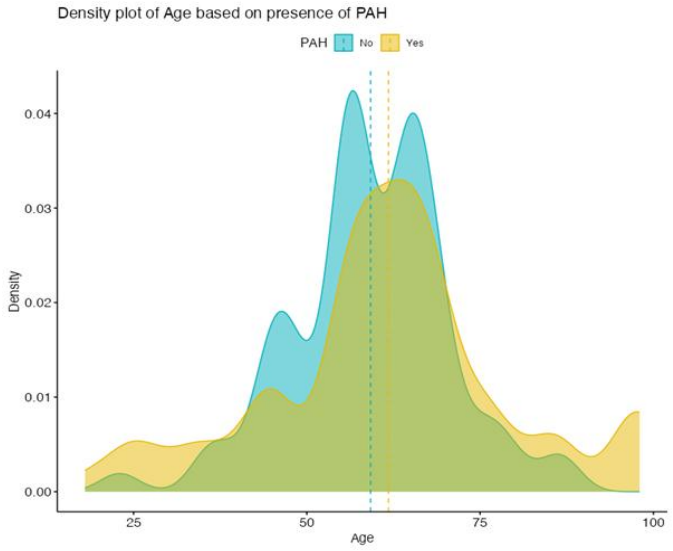


Fig 7: Density distribution of age and presence of pulmonary hypertension

Table 10: Association between gender of participants and presence of pulmonary hypertension

	No PAH n = 73	With PAH n = 77	p-value
Male (n, %)	42, 48.8	44, 51.2	.96
Female (n, %)	31, 48.4	33, 51.6	

Participants' gender was not associated significantly with the presence of PAH with p-value .96.

Table 11: Haemoglobin level and presence of pulmonary hypertension

	No PAH n = 73	With PAH n = 77	p-value
Haemoglobin (Mean (SD))	11.4 (1.7)	8.9 (2.1)	<.001

Participants without PAH had higher haemoglobin level than those with PAH and the difference was statistically significant with p-value <.001.

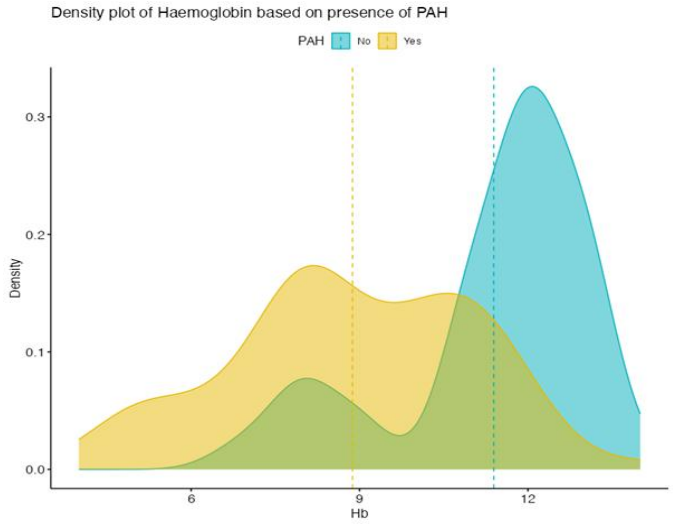


Fig 8: Density distribution of haemoglobin and presence of pulmonary hypertension

Table 12: Left ventricular ejection fraction and presence of pulmonary hypertension

	No PAH n = 73	With PAH n = 77	p-value
LV EF (Mean (SD))	64.8 (1.4)	64.9 (1.0)	.61

Participants' LV ejection fraction was not associated significantly with the presence of PAH with p-value .61.

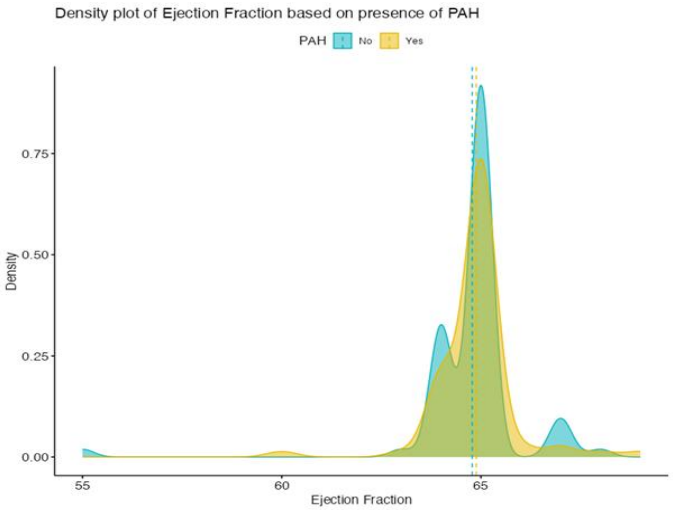


Fig 9: Density distribution of ejection fraction and presence of pulmonary hypertension

Table 13: Association between need for dialysis and presence of pulmonary hypertension

Need for dialysis	No PAH n = 73	With PAH n = 77	p-value
Dialysis dependent (n, %)	5, 18.5	22, 81.5	<.001
Not on dialysis (n, %)	68, 55.3	55, 44.7	

Participants who were depended on dialysis had a higher prevalence of PAH (81.5%) compared to those not on dialysis (44.7%) and the difference was statistically significant with a p-value <.001.

Table 14: Association between stage of CKD and presence of pulmonary hypertension

Stage of CKD	No PAH n = 172	With PAH n = 77	p-value
3 (n,%)	4, 80.0	1, 20.0	<.001
4 (n,%)	37, 84.1	7, 15.9	
5 (n, %)	32, 31.7	69, 68.3	

Participants who were on stage 3 and stage 4 of CKD had lower prevalence of PAH (20.0%and15.9%) compared to those who were on stage 5 CKD (68.3%) and the difference was statistically significant with a p-value <.001.

Discussion

In the present hospital based cross-sectional study conducted among the patients in the wards and OPD of government medical college Ernakulam during March 2021-february 2022 total number of participants were 150

Total number of participants was 150 out of which 86 were male (57%) gender was not associated significantly with pulmonary hypertension with a P-value of 0.96. In this study mean age of the study population was 60.5 years, age was not associated significantly with presence

of pulmonary hypertension with a P-value of 0.29. Out of the 150 participants majorityie, 103 (68.7%) belonged to lower socio-economic class of BG Prasad classification.

Of the 150 patients we have seen comorbid conditions which are CAD, CVA, HTN, DM, DLP of which most common comorbid condition was DM with a prevalence of 90.7%. Similar results were obtained from the study of Andrew et al(1),Leila R et al(2)

Main clinical features present among patients were pedal oedema, anasarca, reduced urinary output, abdominal distension, breathlessness of which most common was pedal oedema with a prevalence of 56.7%

Haemodynamic parameters of patients were taken into consideration, systolic blood pressure,diastolic blood pressure, pulse rate,SpO2 were taken mean of the variables were 133.2,86.6,83.8,98.2 respectively

Of the 150 participants 27(18%) were under dialysis and the rest were managed conservatively

Mean creatinine of the150 participants was 5.6

Out of 150 there were 5 participants belonging to stage 3,44 of stage 4, 101 of stage 5. Of the total population taken for our analysis, 67% belonged to stage 5 CKD.

Haemoglobin value of the participants was used in this study.Mean value was 10.1.It was seen that participants without pulmonary hypertension had higher HB level with mean value of 11.4 compared to those with pulmonary hypertension with a mean value HB of 8.9 and the result was statistically significant with a p value <.001 similar results were obtained from the study conducted by Sankar D. Navaneethan et al (3)

We have excluded patients with LV dysfunction from our study hence Ejection fraction was statistically insignificant with pulmonary hypertension in our study.

Participants who were on stage 3 and 4 of CKD had lower prevalence of pulmonary hypertension at20% and 15 % respectively compared to those who were on stage 5 which is 68% and the results is statistically significant. Similar results were obtained from the studies conducted by D. Navaneethan et al(3),Meghan E. Sise et al(4) these studiesshowed, the prevalence of pulmonary hypertension is significantly high in stage 5 CKD patients compared to other stages

Patients who are on dialysis has a higher prevalence of pulmonary hypertension 81% compared to those not on dialysis 44% and the difference is statistically significant with a P-value of <.001. Here dialysis appears to be a risk factor for developing PH in CKD patients. Similar results were also obtained in the study conducted by Meghan E. Sise et al(4)

Conclusion

1. The estimated prevalence of pulmonary hypertension in CKD stage 5 patients was high compared to stage 3 and stage 4, even after excluding LV dysfunction and other independent risk factors causing development of pulmonary hypertension.
2. The estimated prevalence of pulmonary hypertension is high among dialysis patients compared to that not on dialysis. A statistically significant correlation obtained between those on dialysis and pulmonary hypertension.
3. In patients with CKD, mean haemoglobin concentration among those with pulmonary hypertension is less compared to those without pulmonary hypertension.
4. There was no significant correlation between pulmonary hypertension in CKD with age or gender.

Limitations

Since this study was a hospital based cross sectional study there were no controls to compare with healthy individuals

Because of the limitation of the sample size in the present study further studies will be necessary to determine the correlation between platelet indices and progression of CKD

Effect of peritoneal dialysis on pulmonary hypertension could not be studies as PD patients were not included in this study

Invasive procedure to determine the pulmonary hypertension was not used in this study

Ethics approval

The study was approved by the institutional ethics committee

Consent

I voluntarily give full consent to participate in the study "Proportion of PAH in chronic kidney disease patients" conducted by Dr ELSU BEJOY in the department of Medicine Gov Medical College Ernakulam for the purpose of thesis. I understand that the ECHO CARDIOGRAM and blood investigations reports are used for the study, I need not take the financial burden for the same. I am also aware that by participating in this study, I will not be exposed to any physical and mental harm. I fully understand that my identity will not be exposed at any stage of the study. I understand that my refusal to participate or withdraw from study will not affect my treatment.

List of abbreviations

ACR - Albumin Creatinine Ratio

ADMA - Asymmetric Dimethyl Arginine

AER - Albumin Excretion Rate

AV Access - Arterioveneous Access

CHF - Congestive Heart Failure

CO - Cardiac Output

CVD - Cardio Vascular Disease

ESRD - End Stage Renal Disease

eGFR -Estimated Glomerular Filtration Rate

HD – Haemodialysis

KDIGO - Kidney Disease Improving Global Outcomes

NO - Nitric Oxide

PAP - Pulmonary Artery Pressure

PASP - Pulmonary Artery Systolic Pressure

PCWP - Pulmonary Capillary Wedge Pressure PVR - Pulmonary Vascular Resistance

VTE - Venous Thromboembolism

Author's contribution

EB collected, analysed and interpreted the patient data required for the study, The study was guided through out by JG, AJ,JKJ and FK and were major contributors in writing the manuscript. All authors read and approved the final manuscript

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First and foremost, I am thankful to God Almighty for giving me the strength, knowledge, ability and opportunity to undertake this study and complete it satisfactorily.

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