“OUTCOME OF PULMONARY HYPERTENSION IN POST RENAL TRANSPLANT RECIPIENT”

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF

THE REGULATIONS FOR THE

AWARD OF DM IN NEPHROLOGY

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PSG INSTITIUTE OF MEDICAL SCIENCES AND RESEASRCH

THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY, CHENNAI

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CERTIFICATE

PSG Institute of Medical Sciences & Research

Coimbatore

This is to certify that **Dr. N.SIVA** has prepared this dissertation entitled **"OUTCOME OF PULMONARY HYPERTENSION IN POST RENAL TRANSPLANT RECIPIENT"** under my overall supervision and guidance in PSG Institute of Medical Science and Research, Coimbatore in partial fulfillment of the regulations of The TamilNadu Dr. M.G.R Medical University for the award of DM Neurology.

DR.G.VENU MD, DM.,
Professor and Head of the Department
Department of Nephrology
PSG IMS & R

DR.S. RAMALINGAM MD.,
Principal
PSG IMS & R

Place: Coimbatore

Date:

DECLARATION

I hereby declare that dissertation entitled **"OUTCOME OF PULMONARY HYPERTENSION IN POST RENAL TRANSPLANT RECIPIENT"** was prepared by me under the guidance and supervision of **Dr. G.VENU MD, DM,** PSG IMS&R, and Coimbatore. The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the University Regulations for the award of DM degree in Neurology. This dissertation has not been submitted for the award of any Degree or Diploma.

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CONTENTS

INTRODUCTION

Pulmonary hypertension is characterized by increased pulmonary arterial pressure and secondary right ventricular failure. It is progressive, if untreated it turns fatal and rate of progression is high among renal failure patients. The prevalence of chronic kidney disease in developed world is 13%[1].Both the complication worsens one another, if they co-exist.

Classification of PH has gone through various changes and in 1998 PAH group have concluded with Group 1, 2, 3, 4, and 5, which was approved by WHO[2].

According to WHO classification pulmonary artery hypertension has 5 categories. Usually it is done by right heart catheterization and the non invasive method is Doppler echocardiography study. The echocardiography parameters taken into account are right ventricular size, thickness and function, valve anatomy and functions.

The maximum tricuspid regurgitant jet velocity is recorded and the pulmonary artery systolic pressure (PASP) is then calculated:

$$PASP = (4 \times TRV \text{ squared}) + RAP$$

TRV is the maximum tricuspid regurgitant jet velocity and RAP is the right atrial pressure estimated from the size and respiratory variation of flow in the inferior vena cava.

Doppler echocardiography of limited value when an adequate tricuspid regurgitant jet cannot be sampled.[3]

Patients with PHT may have echocardiography signs of right ventricular pressure overload, including paradoxical bulging of the septum into the left ventricle during systole and hypertrophy of the right ventricular free wall and trabeculae.

As the right ventricle fails, there is dilation and hypokinesis, septal flattening, right atrial dilation, and tricuspid regurgitation. The tricuspid regurgitation, a secondary manifestation of dilation of the tricuspid annulus and right ventricle and not due to intrinsic valve abnormality[4]. Other findings associated with pulmonary hypertension are pulmonic insufficiency and mid systolic closure of the pulmonic valve[5].

The echocardiography findings of PHT are summarized in the figure.

Based upon a Doppler echocardiography study[7], it can be determined if PHT is likely, unlikely, or possible[6]:

1. PHT is likely if the PASP is >50 and the TRV is >3.4

2. PHT is unlikely if the PASP is ≤36, the TRV is ≤2.8, and there are no other suggestive findings.

   PHT is possible with other combinations of findings

One of limitation of Doppler echocardiography is that it may be misleading, when patient's inadequate tricuspid regurgitation jet is over-interpreted.

WHO Diagnostic Classification of Pulmonary Hypertension[7]

Class	Definition	Conditions
I	Idiopathic, familial, and associated PAH	Connective tissue diseases, HIV infection, congenital heart disease, portal hypertension and pulmonary veno-occlusive disease, drugs and toxins.
II	PH associated with left-sided heart disease	Left-sided heart systolic dysfunction, left-sided heart diastolic dysfunction, left-sided valvular disease (mitral and/or aortic)
III	PH associated with lung diseases and/or hypoxia	COPD, interstitial lung disease, sleep apnea
IV	Chronic thromboembolic PH	Obstruction of pulmonary arterial vessels (proximal or distal) by thromboemboli, tumors, or foreign bodies
V	PH with unclear or multifactorial causes	Dialysis-dependent CKD; several hematologic, systemic, and metabolic disorders; miscellaneous

Note: Class I PH formerly was referred to as pre capillary PH; class II, as post capillary PH.

PH in CKD patients on maintenence haemodialysis is likely to have worse prognosis, and unless found earlier and worked up for Renal transplant and undergone renal transplant at the earliest, it can’t be reverted. Therefore, in this study effect of renal transplant on PH and its outcome is done by Doppler echocardiography in pre transplant and post transplant period during 3^{rd} and 6^{th} month.

AIM AND OBJECTIVES

To find the status of pulmonary hypertension present in the pre transplant period after 3rd and 6th month of renal transplantation using Doppler echocardiography

REVIEW OF LITERATURE

Chronic kidney disease (CKD) is a heterogeneous group of disorders resulting in number of changes both structural and functional abnormalities, or both persisting for minimum of 3months or more. Abnormality in urine with proteinuria or hematuria and structure or histological features, with or without fall in GFR <60mL/min/1.7m2. CKD is divided into five stages according GFR and Albuminuria by KDIGO 2012[9].

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m^2) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

GFR stage 3 CKD (a GFR of 30 to 59mL /min per 1.73 m^2) has been subdivided into GFR stages 3a and 3b to more accurately; patients on dialysis are sub classified as GFR stage 5D.

Albuminuria — The three Albuminuria stages follow as "normal", "high","very high" this grading is considered because of its high predictive of mortality. With consideration of relative risk and general outcome GFR and ACR stages was established. Based upon these findings, a "heat map" can be constructed that divides patients with CKD[10].

Moderate risk (yellow) — 73 percent of patients with CKD

High risk (orange) — 18 percent of patients with CKD

Very high risk (red) — 9 percent of patients with CKD

Both Albuminuria and GRF goes hand on hand both can be used together for a patient progress on CKD. Evaluation of GFR serum creatinine and a GFR estimation equation is required, other additional test which are used is used cystatin C or a clearance method. But it should be done in properly calibrated lab and also a clinical assessment, regardless of age, sex, and degree of proteinuria or Albuminuria. The estimation of eGFR is required to improve the management of common disease in the population[11].

METHODS OF ESTIMATION GFR:[8,9,10,11]

1. Cockcroft-Gault equation — The Cockcroft-Gault equation allows the creatinine clearance to be estimated from the serum creatinine in a patient with a stable serum creatinine.
2. MDRD study equations — several equations were derived from data on adult patients enrolled in the MDRD with six-variable equation initially and then with four variables. GFR measured at baseline using urinary clearance of iothalamate.
3. CKD-EPI is a gold standard and superior when GFR is normal or mildly reduced — The CKD-EPI equation was developed with the data pooled from 10 studies to provide a more accurate estimate of GFR among individuals with normal or only mildly reduced GFR (ie, above 60 mL/min per 1.73 m^2)

Equations for Estimating GFR

Cockroft-Gault formula[5]

Male C_{cr} (ml/min) = $\frac{(140 - \text{age}) \times \text{weight}}{72 \times S_{cr}(\text{mg/dl})}$ or C_{cr} (ml/min) = $\frac{(140 - \text{age}) \times \text{weight}}{0.814 \times S_{cr}(\mu\text{mol/l})}$

Female C_{cr} (ml/min) = $\frac{(140 - \text{age}) \times \text{weight} \times 0.85}{72 \times S_{cr}(\text{mg/dl})}$ or C_{cr} (ml/min) = $\frac{(140 - \text{age}) \times \text{weight} \times 0.85}{0.814 \times S_{cr}(\mu\text{mol/l})}$

MDRD study equation (four-variable equation)[7]

GFR (ml/min/1.73 m^2) = $186 \times S_{cr}$ (mg/dl)$^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if black)

or

GFR (ml/min/1.73 m^2) = $32{,}788 \times S_{cr}$ (μmol/l)$^{-1.154} \times \text{Age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if black)

MDRD Study Equation for Use with Standardized Serum Creatinine (Four-variable equation)[7]

GFR (ml/min/1.73 m^2) = $175 \times$ Standardized S_{cr}(mg/dl)$^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if black)

or

GFR (ml/min/1.73 m^2) = $30{,}849 \times$ Standardized S_{cr}(μmol/l)$^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times 1.210$ (if black)

CKD-EPI Equation for Use with Standardized Serum Creatinine[12]

GFR (ml/min/1.73 m^2) = $141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) $\times 1.157$ (if black)

where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.

Female	$\leq 0.7 \rightarrow \text{GFR} = 144 \times (S_{cr}/0.7)^{-0.329}$ $> 0.7 \rightarrow \text{GFR} = 144 \times (S_{cr}/0.7)^{-1.209}$	$\times (0.993)^{\text{Age}}$	$\times 1.157$ (if black)
Male	$\leq 0.9 \rightarrow \text{GFR} = 141 \times (S_{cr}/0.9)^{-0.411}$ $> 0.9 \rightarrow \text{GFR} = 141 \times (S_{cr}/0.9)^{-1.209}$		

*Age in years, weight in kg, S_{cr}, serum creatinine

NATURAL HISTORY OF RENAL DISEASE:

The initial injury to the kidney results in various forms ranging from asymptomatic hemauria to CKD on MHD. Poststreptococcal glomerulonephritis in children or lupus in some patient with repeated insult to kidneys lead to permanent damage.

Kidney has a special ability of **'Adaptive Hyperfiltration'** process which patient can have mild renal failure or near normal creatinine. Additional homeostasis mechanism helps total body water, sodium potassium, calcium and phosphorus remains normal[12].

ESRD INCIDENCE AND PREVALENCE:

Lack of proper maintenance of registry, makes an inaccurate estimation, so estimation is made from RRT in hospitals. Many patients are not aware of the disease, with no medical attestation, estimates has shown 55,000 patients on RRT. Dialysis population will annually about 10-20%.

Gender in CKD: Women generally have 10-15% les Nephron number[13]. The rate of difference in the incidence and prevalence is by glomerular mass, response to hormones, cytokines and other circulating factors also with aging and reduction in Nephron number.

Complication of CKD:

1. Reversible causes of renal failure:
    a. Decreased renal perfusion
    b. Administration of nephrotoxic drugs
    c. Urinary tract obstruction

2. Slowing the rate of progression
    a. Principal targets for renal protection
    b. Other targets for renal protection
3. Treatment of the complications of renal failure
    a. Volume overload
    b. Hyperkalemia
    c. Metabolic acidosis
    d. Mineral and bone disorders (MBD)
    e. Hypertension
    f. Anaemia
    g. Dyslipidemia
    h. Sexual dysfunction
4. Treatment of complications of ESRD
    a. Malnutrition
    b. Uremic bleeding
    c. Pericarditis
    d. Uremic neuropathy
    e. Thyroid dysfunction
5. Cardiovascular risk factor

CARDIOVASCULAR RISK IN CKD ON MHD:

Traditional risk: Smoking, Hypertension, Diabetes, Dyslipidemia, Old Age are highly prevalent in CKD group.

Non traditional risk factors: Uraemia, Anaemia, Elevated Cytokines, Increased Calcium Intake, Abnormality in Bone Metabolism, Nutritional Status.

PULMONARY HYPERTENSION IN CKD:

Introduction:

PH has gone through a series of change since the first version was proposed in 1973 at the first international conference on primary pulmonary hypertension endorsed by the World Health Organization. Till fourth World Symposium on PH held in 2008 in Dana Point, California, and approved by WHO. During the last 2 decades mild to moderate forms of PH has become more common. Pulmonary hypertension in chronic kidney disease patient is not associated with connective tissue disorder or a systemic disease; decrease in renal function can be a trigger for the development of pulmonary hypertension in CKD population.

A clinical history and clinical manifestation and etiology will be reliable on PH. Pressure overload on RV (right ventricle) leads to increase in dilatation and hypertrophy of RV. This may progress and lead to TR

tricuspid regurgitation and atrial dilatation. Pulmonary hypertension initially can be managed medically, but with CKD stage V on haemodialysis renal transplant will be a better option.

EPIDEMIOLOGY:

A large survey documented in US that pulmonary hypertension during two decades 1980-2002 had death rate ranges from(5.2-5.4/100,000).

The prevalence of group 1 PAH in the general population is estimated to be 5 to 15 cases per one million adults[15].

Definitions:

For the Diagnosis and Treatment of Pulmonary Hypertension in year 2008 a team of group worked that are the European Society of Cardiology (ESC), the European Respiratory Society (ERS) and International Society of Heart and Lung Transplantation (ISHLT).

Accordingly Pulmonary hypertension (PH) is a hemodynamic and path physiological condition defined as an increase in mean pulmonary arterial pressure (PAP) -25 mmHg at rest as assessed by right heart catheterization.

NOMENCLATURE:

1. Pulmonary arterial hypertension (PAH) refers to group 1 PAH.
2. Pulmonary hypertension (PH) refers to any of group 2 PH through group 5 PH.
    a. The definition of PH on exercise as a mean PAP 30 mmHg as assessed by right heart catheterization is not supported by published data.
    b. Pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterized by the presence of pre-capillary PH in the absence of other causes of pre-capillary PH such as PH due to lung diseases, chronic thromboembolic PH, or other rare diseases.

PAH includes different forms that share a similar clinical picture and virtually identical pathological changes of the lung microcirculation.

Haemodynamic definitions of pulmonary hypertension[16]

Definition	Characteristics	Clinical group(s)[b]
Pulmonary hypertension (PH)	Mean PAP ≥25 mmHg	All
Pre-capillary PH	Mean PAP ≥25 mmHg PWP ≤15 mmHg CO normal or reduced[c]	1. Pulmonary arterial hypertension 3. PH due to lung diseases 4. Chronic thromboembolic PH 5. PH with unclear and/or multifactorial mechanisms
Post-capillary PH	Mean PAP ≥25 mmHg PWP >15 mmHg CO normal or reduced[c]	2. PH due to left heart disease
Passive	TPG ≤12 mmHg	
Reactive (out of proportion)	TPG >12 mmHg	

CLASSIFICATION OF PULMONARY HYPERTENSION:[17]

Group 1 PAH: Pulmonary arterial hypertension (PAH).

These include connective tissue diseases,

- HIV infection
- Portal hypertension
- Congenital heart disease,
- Schistosomiasis
- Chronic hemolytic anemia
- Persistent pulmonary hypertension of the newborn,
- Pulmonary veno-occlusive disease,
- Pulmonary capillary hemangiomatosis
- Drug- and toxin-induced PAH (aminorex, fenfluramine, dexfenfluramine, and toxic rapeseed oil)
- Selective serotonin reuptake inhibitors.

Group 2 PH: Pulmonary hypertension owing to left heart disease.

Elevated left atrial and pulmonary venous pressure (pulmonary venous hypertension).

- Systolic dysfunction
- Diastolic dysfunction

- Valvular heart disease

Group 3 PH: Pulmonary hypertension with lung diseases or hypoxemia.

- Chronic obstructive pulmonary disease
- Interstitial lung disease, pulmonary diseases with a
- Mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Causes of hypoxemia.

Group 4 PH: Chronic thromboembolic pulmonary hypertension

- PH due to thromboembolic occlusion of the proximal or distal pulmonary vasculature.

Group 5 PH: Pulmonary hypertension with unclear multifactorial mechanisms.

- Hematologic disorders (eg, myeloproliferative disorders)
- Systemic disorders (eg, sarcoidosis)
- Metabolic disorders (eg, glycogen storage disease)
- Miscellaneous causes (eg, sickle cell disease, beta-thalassemia).

WHO CLASSIFICATION:

WHO diagnostic classification of pulmonary hypertension

Class	Definition	Conditions
I	Idiopathic, familial, and associated PAH	Connective tissue diseases, HIV infection, congenital heart disease, portal hypertension and pulmonary veno-occlusive disease, drugs and toxins.
II	PH associated with left-sided heart disease	Left-sided heart systolic dysfunction, left-sided heart diastolic dysfunction, left-sided valvular disease (mitral and/or aortic)
III	PH associated with lung diseases and/or hypoxia	COPD, interstitial lung disease, sleep apnea
IV	Chronic thromboembolic PH	Obstruction of pulmonary arterial vessels (proximal or distal) by thromboemboli, tumors, or foreign bodies
V	PH with unclear or multi factorial causes	Dialysis-dependent CKD; several hematologic, systemic, and metabolic disorders; miscellaneous

Who classifies PH in 5 groups. Its generally measured by mean pulmonary artery pressure ≥25 mm Hg at rest, done by right cardiac catheterization for group I pulmonary wedge pressure ≤ 15mm Hg .

Non invasive method also estimates pulmonary hypertension by Doppler echocardiography, measurement of PASP (pulmonary artery systolic pressure) will be recorded in physiological condition. Studies revels that pulmonary hypertension is considered when PASP ≥ 50 mm Hg and or TRV is faster than 3.4m/s. PASP values of 35-29 and TRV values 2.8 – 3.4 m/s considered most probable when PASP is ≥ 50mmHg.

1 Pulmonary arterial hypertension (PAH)

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2
  - 1.2.2 ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
  - 1.2.3 Unknown
- 1.3 Drugs and toxins induced
- 1.4 Associated with (APAH)
  - 1.4.1 Connective tissue diseases
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
  - 1.4.6 Chronic haemolytic anaemia
- 1.5 Persistent pulmonary hypertension of the newborn

1′ Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

2 Pulmonary hypertension due to left heart disease

- 2.1 Systolic dysfunction
- 2.2 Diastolic dysfunction
- 2.3 Valvular disease

3 Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental abnormalities

4 Chronic thromboembolic pulmonary hypertension

5 PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders: myeloproliferative disorders, splenectomy.
- 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4 Others: tumoural obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

PH AND CKD:

Chronic kidney disease increases the incidence of various diseases, commonest one is cardiovascular disease. Mortality is high in this group along with CKD G5D. Chronic kidney disease is associated commonly with DM, SHT, and CAD with LV dysfunction, majority having diastolic dysfunction. Apart from this chronic kidney disease may also be associated with pulmonary hypertension commonly in haemodialysis population.

The CKD PH is mainly a retrospective study in US population. Right sided cardiac catheterization is a definitive modality of investigation for PH by international group recommendations. Measurement of PASP in CKD G5D is mainly done by Doppler echocardiography which is a non invasive method. There is several potential explanations for the development of PH, hormonal and metabolic factors which lead to pulmonary arterial vasoconstriction and increase pulmonary vascular resistance [19, 20, 21].

PROGNOSTIC FACTORS:

Data from prospective trials suggest that the following factors shows a poorer prognosis in patients with PAH[23]

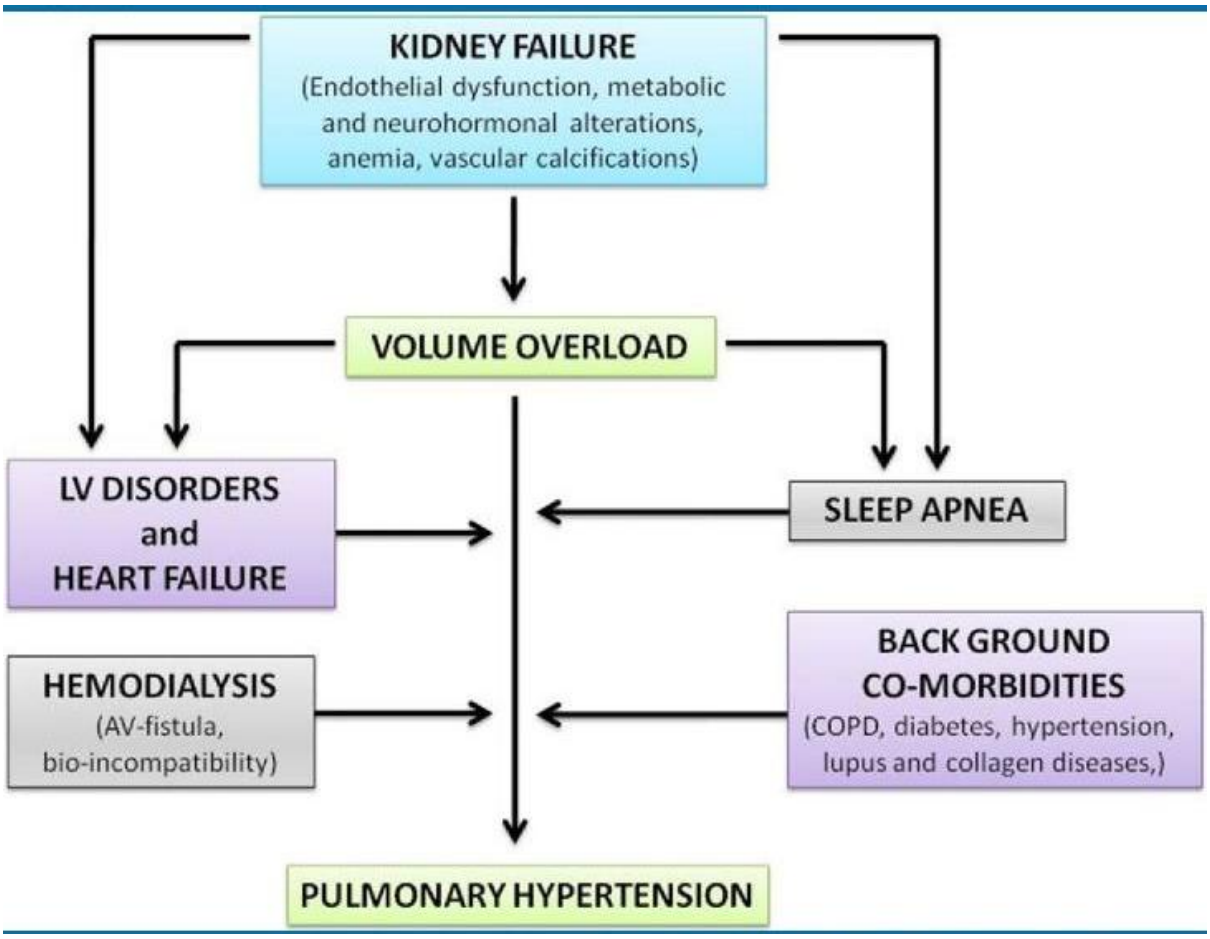
1. Age >45 years
2. Failure to improve during treatment.
3. Echocardiography findings.
4. Decreased pulmonary arterial capacitance
5. Poor right ventricular contractile reserve
6. Increased N-terminal pro-brain natriuretic peptide level (NT-pro-BNP
7. Prolonged QRS duration
8. Hypocapnia
9. Co morbid conditions (e.g. , COPD, diabetes)

PATHOPHYSIOLOGY OF PH:

The pulmonary vascular endothelium is mono layer, which regulates the vascular tone. There will be release of nitric oxide and prostacylin which help in inhibition of platelet aggregation and vasodilator and vasoconstriction by Endothelin1 (ET-1) in physiological state.

Conditions associated with pulmonary hypertension causes reduction of prostaglandin and nitric oxide (NO) and increased Thromboxane, endothelin and serotonin which stimulate the endothelial and smooth muscle cell proliferation. Apart from this increase in collagen synthesis and platelet aggregation also plays a role in PH.

The main mechanism associated with pulmonary hypertension is Endothelial Dysfunction[25] it is the main trigger which is linked with CKD population. High levels of endothelin1 and reduced production of nitric oxide (NO) in haemodialysis population predisposes to pulmonary hypertension[24].



Patient on heamodialysis will have overproduction of endogenous Asymmetric Dimethylarginine (ADMA) which is the inhibitor of NO. The uremic toxins potentially enhances the formation of ADMA in CKD G5D population[26,27]. Davide et al discussed the pathophysiology of Pulmonary Hypertension in CKD population.

METHODOLOGY

Study method

The study was conducted on patients who underwent renal transplantation in Department of Nephrology PSGIMSR. Patients with pulmonary hypertension pre transplant were taken up for the study after the application of inclusion and exclusion criteria and after obtaining consent.

Demographic, clinical information and laboratory results were collected. The assessment of PH was done by Doppler echocardiography pre transplant and 3 and 6 months after transplant during follow up.

Echocardiography

Echocardiography is performed in all patients during 3&6 month of follow up. The major role of echocardiography is to estimate the pulmonary artery systolic pressure and to assess right ventricular size, thickness, and function.

Minor roles are to assess right atrial size, left ventricular systolic and diastolic function, valve function, pericardial effusions and intra cardiac shunts.

Echocardiography is performed using sector array probe using ultrasonic wave.

The maximum tricuspid regugatation jet velocity is recorded and the pulmonary artery systolic pressure (PASP) is calculated by using the formulae

PASP = (4 x TRV squared) + RAP

Where,

TRV- maximum tricuspid regurgitant jet velocity,

RAP - right atrial pressure which is estimated from the size and respiratory variation of flow in the inferior vena cava.

Doppler echocardiography is limited when an adequate tricuspid regurgitant jet cannot be sampled. Echocardiography signs of PHT includes right ventricular pressure overload, paradoxical bulging of inter ventricular septum into the left ventricle during systole and hypertrophy of the right ventricular free wall and trabeculae. As the right ventricle fails, there is dilation and hypokinesis, septal flattening, right atrial dilation, and tricuspid regurgitation.

There is no intrinsic abnormality of the tricuspid valve, tricuspid regurgitation is a secondary manifestation of dilation and hypokinesis, septal flattening, right atrial dilation, dilation of the tricuspid annulus and right ventricle[30].

Other findings associated with pulmonary hypertension are pulmonic insufficiency and midsystolicclosure of the pulmonic valve[31]. The echocardiography findings of PHT are summarized in the figure. Based upon a Doppler echocardiography study, it can be determined if PHT is grouped as - likely, unlikely, or possible[16]:

PHT is likely if the PASP is >50, the TRV is >3.4

PHT is unlikely if the PASP is ≤36, the TRV is ≤2.8, and there are no other suggestive findings,

PHT is possible with other combinations of findings. One of the limitations of Doppler echocardiography is that it may be misleading in the assessment of patients with suspected pulmonary hypertension, especially when an inadequate tricuspid regugatation jet is over-interpreted. This was explained by an observational study of 65 patients with various types of PH[32]. The pulmonary arterial pressure estimated by Doppler

echocardiography was ± 10 mmHg than what was obtained by right heart catheterization in 48 percent of patients.

Overestimation and underestimation of pulmonary arterial pressure occurred with similar frequency, although the magnitude of the underestimation was greater. A major limitation of the study was that catheterization and Doppler echocardiography were not performed simultaneously.

The study supports our opinion that there should be a low threshold to evaluate patients with suspected pulmonary hypertension via right heart via right heart catheterization. Despite its limitations, Doppler echocardiography detects PHT with greater accuracy than clinical history and physical examination.

Study place:

- Conducted with IP/OP clinic of dept of Nephrology in PSG IMS&R Coimbatore.

Study population:

Patient diagnosed with CKD on MHD who has pre transplant workup and renal transplant in hospital done during time period of 3 years will be

included in the study ,based on the inclusion and exclusion criteria . Total number of patients were 75 out of which 55 was included in the study after the application of criteria & after obtaining written informed consent .

Study period:

The study was conducted during the time period of July 2011 – December 2013.

Inclusion criteria:

1. CKD on MHD, who have undergone renal transplantation
2. Mild and moderate Pulmonary hypertension
3. CKD due to all etiologies and patient of all age group were selected.
4. Individuals who obtained consent to participate in the study.

Exclusion Criteria:

1. Not fit for renal transplantation.
2. Sever pulmonary hypertension
3. COPD
4. Parenchymal lung disease
5. Chest wall disease
6. Previous h/o PH
7. Pulmonary embolism
8. Smoker >10 yr duration
9. Collagen vascular Disease
10. Valvular heart disease

Study design:

Cross sectional/ sample – convenience sampling.

Data collection:

Using Questionnaires, chart review for lab values and echocardiography.

Statistical analysis:

1. Descriptive statistic for prevalence of PH undergone renal transplantation.
2. Inferential statistics using non parametric tests for qualitative and ‘t’ Test for Quantitative variables will be carried out.

PROTOCOL

Initial assessment

Patient Clinical history, Family history, Blood group, Duration of illness and RRT

↓

Pre transplant work up

Laboratory parameters, Doppler echocardiography USG abdomen, Renal CT Angiography, DTPA DMSA scan, General assessment (Cardiology, ENT, Ophthalmology, O&G) & fitness

↓

Renal transplantation

↓

Follow Up

Regular Monthly follow up.

3 & 6 months Echocardiography

OBSERVATION AND RESULTS

TABLE.1. INCIDENCE OF PULMONARY HYPERTENSION

Pre- transplant	No of patients	Percentage (%)
No	33	60.0
Yes	22	40.0
Total	**55**	**100.0**

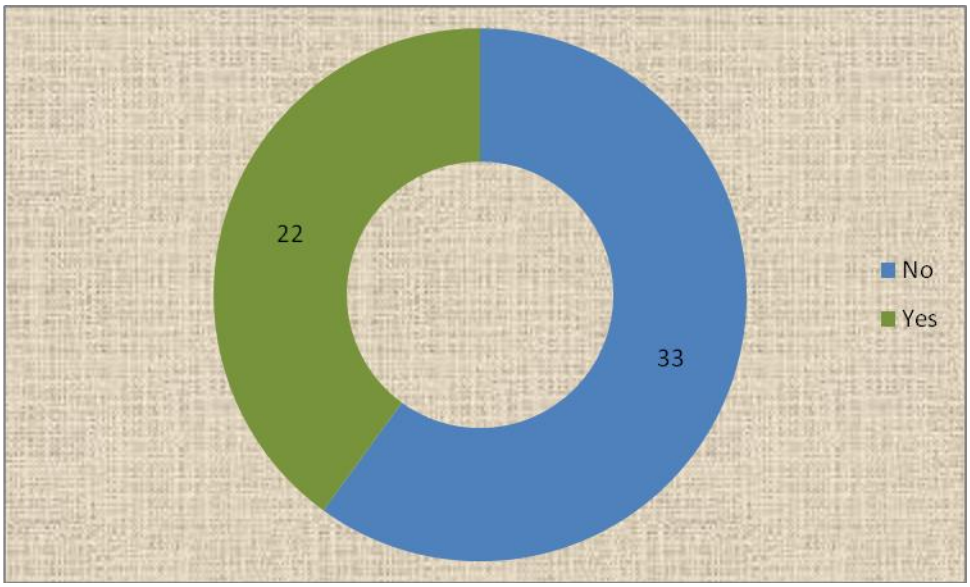


TABLE 2. AGE RATIO

Age	No. of patients	Percentage (%)
<20	2	3.6
21-30	8	14.5
31-40	26	47.3
41-50	12	21.8
51-60	5	9.1
61-70	2	3.6
Total	**55**	**100.0**

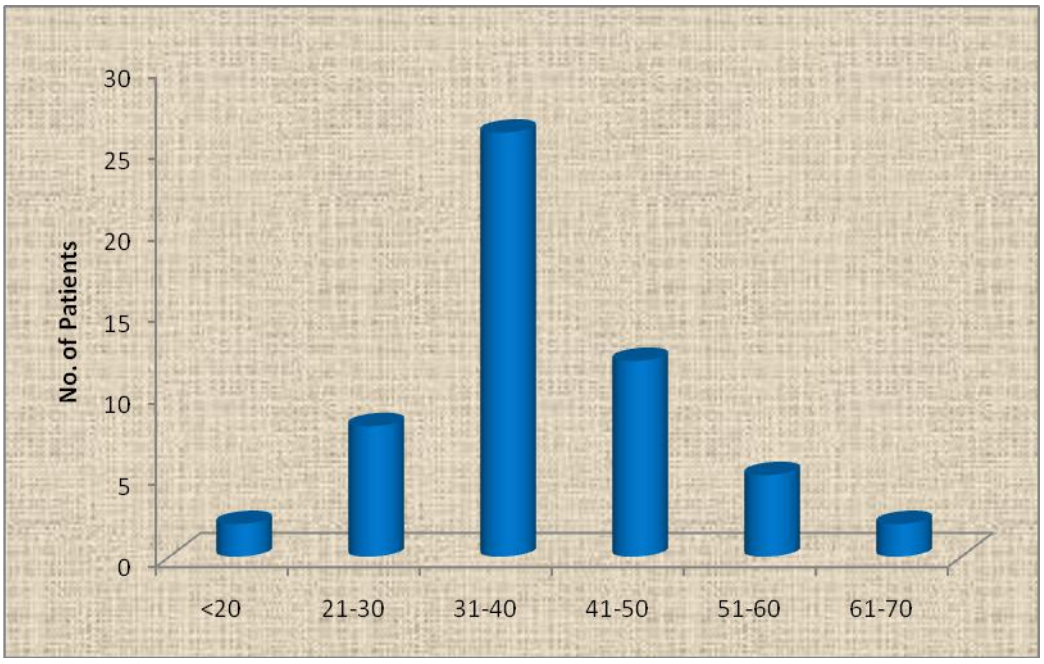


TABLE 3. AGE AND PRE-TRANSPLANT

Age		Pre-transplant			P value
		No	**Yes**	**Total**	
<20	No.	1	1	2	0.017
	%	50.0%	50.0%	100.0%	
21-30	No.	8	0	8	
	%	100.0%	0%	100.0%	
31-40	No.	18	8	26	
	%	69.2%	30.8%	100.0%	
41-50	No.	4	8	12	
	%	33.3%	66.7%	100.0%	
51-60	No.	2	3	5	
	%	40.0%	60.0%	100.0%	
61-70	No.	0	2	2	
	%	0%	100.0%	100.0%	
Total	**No.**	**33**	**22**	**55**	
	%	**60.0%**	**40.0%**	**100.0%**	

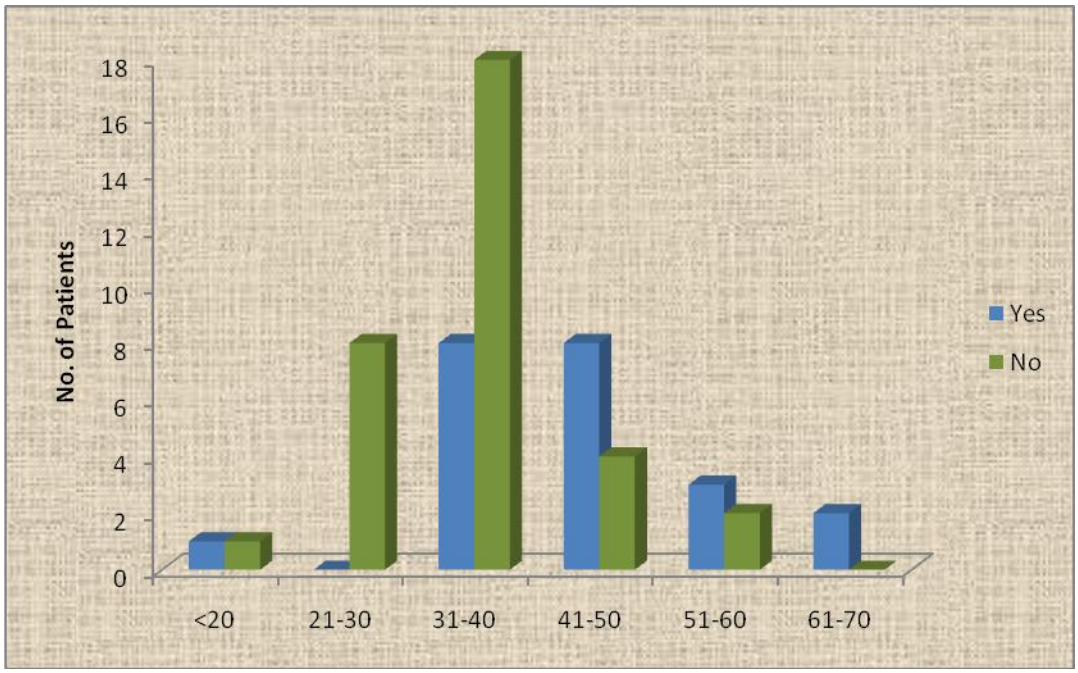


TABLE 4. SEX RATIO AND INCIDENCE

Gender	No. of patients	Percentage (%)
Male	34	61.8
Female	21	38.2
Total	**55**	**100.0**

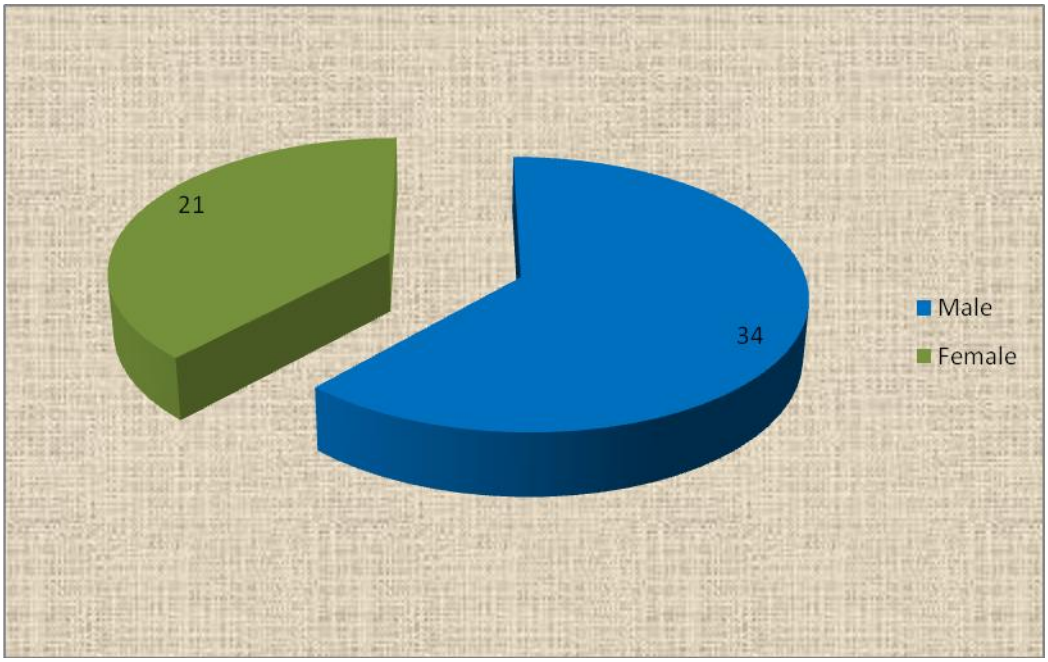


TABLE 5. GENDER AND PRE-TRANSPLANT

Gender		Pre-transplant			P value
		No	Yes	Total	
Male	No.	20	14	34	0.524
	%	58.8%	41.2%	100.0%	
Female	No.	13	8	21	
	%	61.9%	38.1%	100.0%	
Total	**No.**	**33**	**22**	**55**	
	%	**60.0%**	**40.0%**	**100.0%**	

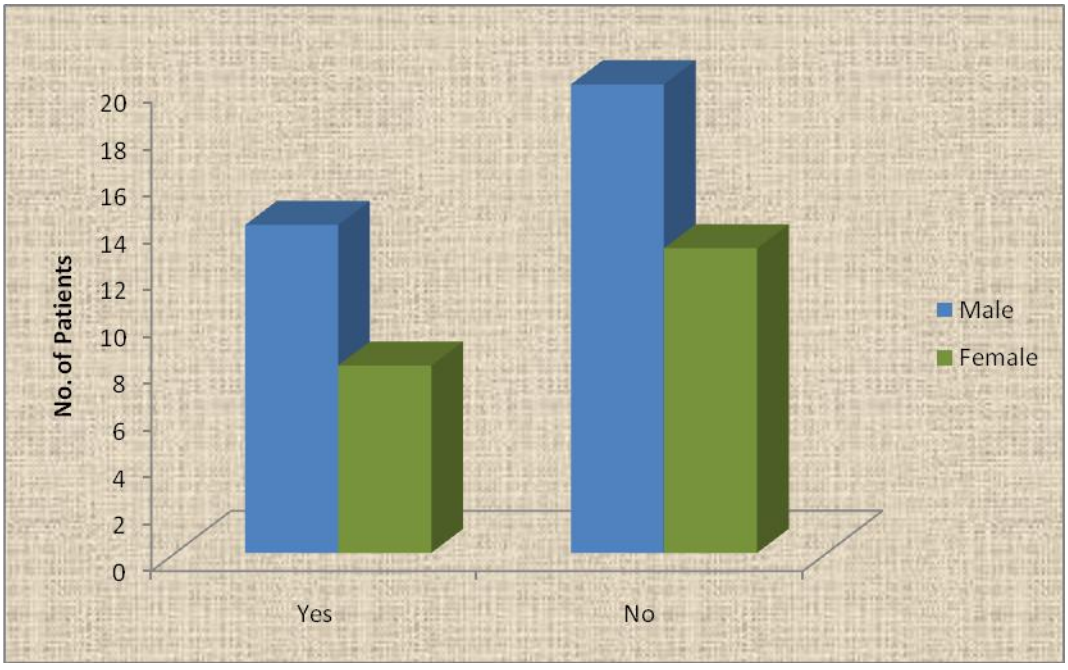


TABLE .6. GENDER RELATION WITH PH

Gender	No of patients	Percentage (%)
Male	7	50.0
Female	7	50.0
Total	14	100.0

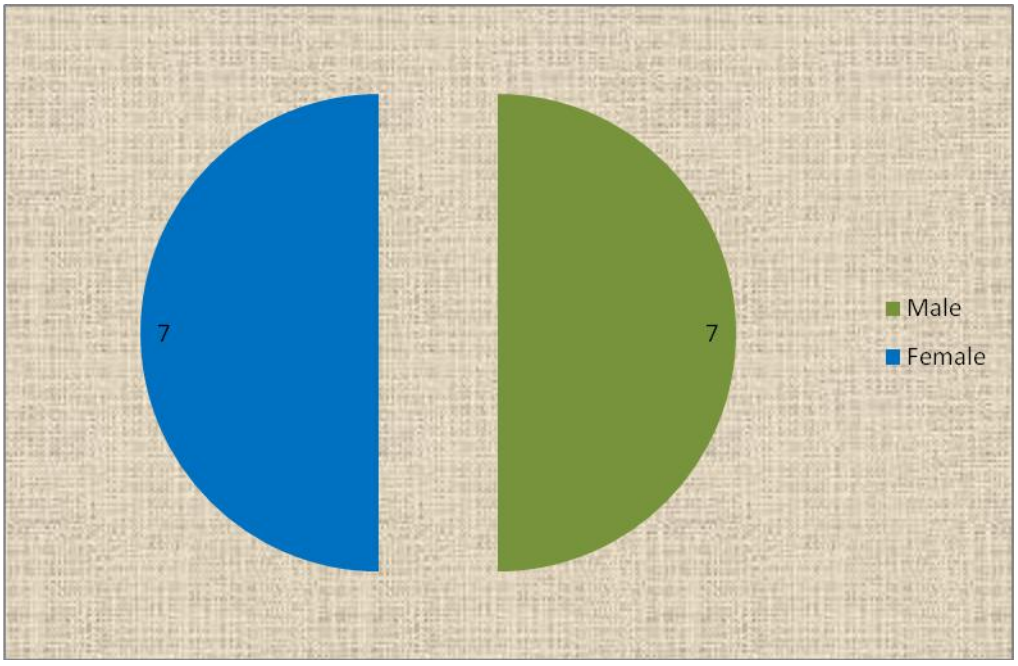


TABLE.7. RELATIONSHIP OF DONOR

Relationship of donor	No. of patients	Percentage (%)
Related	42	76.4
Unrelated	12	21.8
Cadaver	1	1.8
Total	**55**	**100.0**

TABLE 8. HYPERTENSION

Hypertension	No. of patients	Percentage (%)
No	34	61.8
Yes	21	38.2
Total	**55**	**100.0**

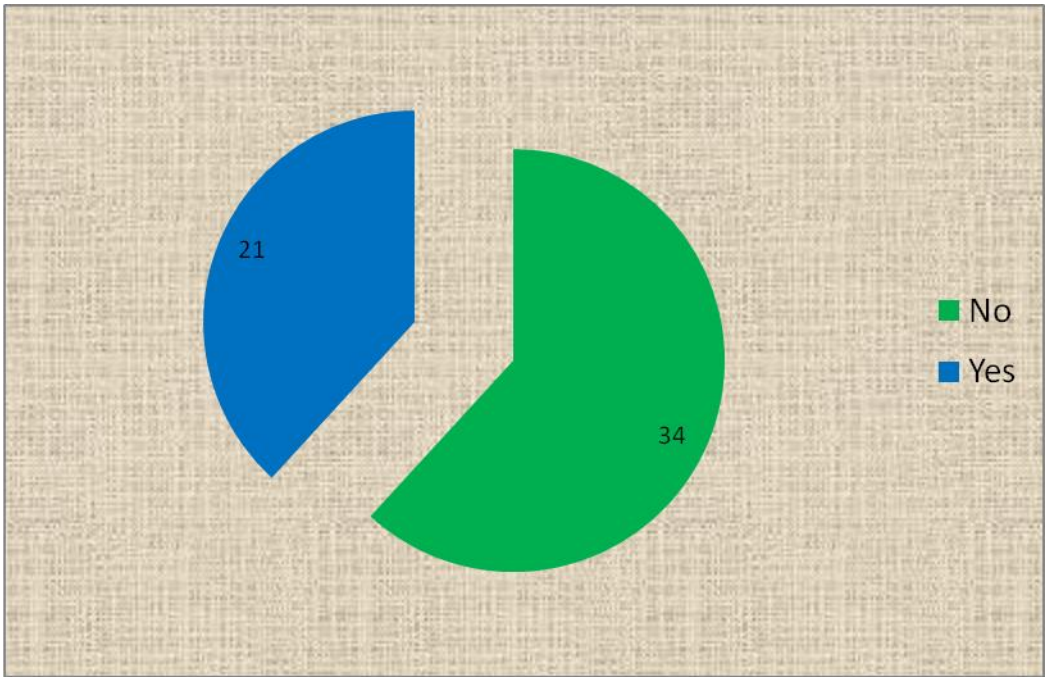


TABLE. 9. HYPERTENSION WITH AGE

Age		SHT			P value
		No	Yes	Total	
<20	No.	1	1	2	0.053
	%	50.0%	50.0%	100.0%	
21-30	No.	8	0	8	
	%	100.0%	0%	100.0%	
31-40	No.	18	8	26	
	%	69.2%	30.8%	100.0%	
41-50	No.	4	8	12	
	%	33.3%	66.7%	100.0%	
51-60	No.	2	3	5	
	%	40.0%	60.0%	100.0%	
61-70	No.	1	1	2	
	%	50.0%	50.0%	100.0%	
Total	**No.**	**34**	**21**	**55**	
	%	**61.8%**	**38.2%**	**100.0%**	

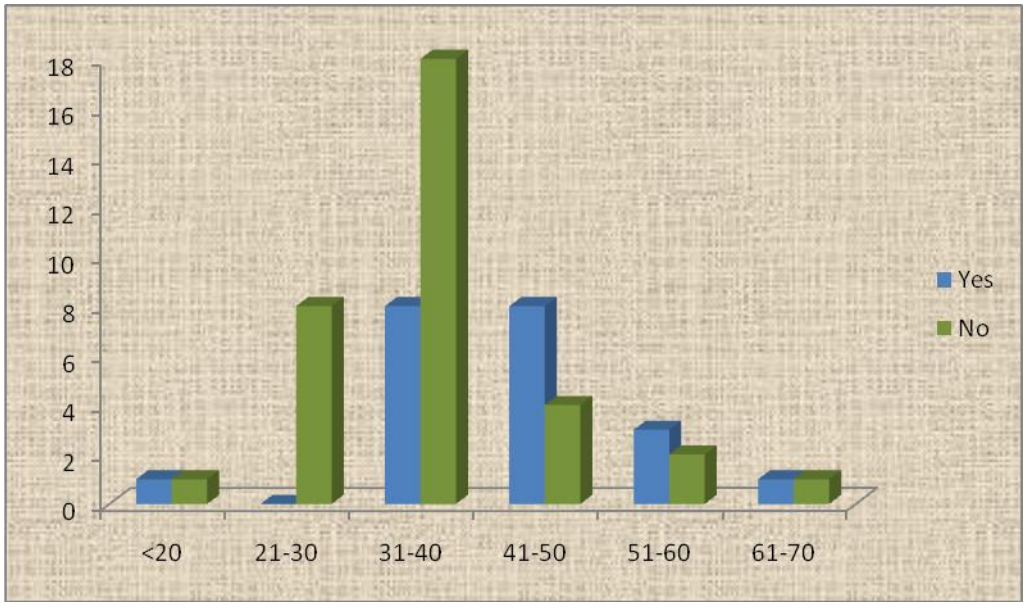


TABLE.10. HYPERTENSION ESRD WITH PH:

SHT	No of patients	Percentage (%)
No	8	57.1
Yes	5	42.9
Total	13	100.0

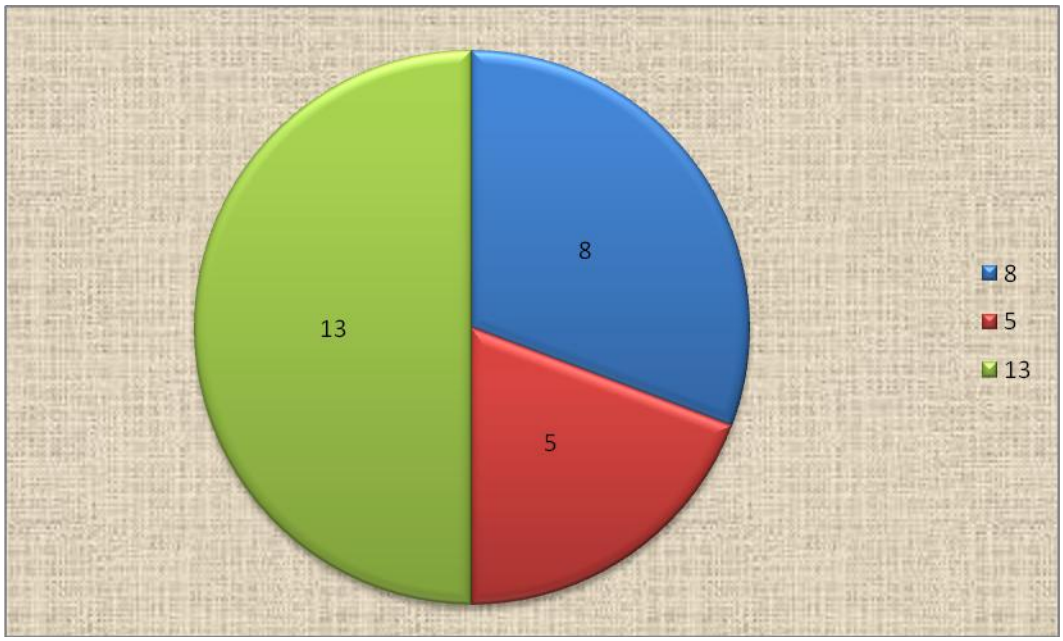


TABLE 11: SHT & PRE TRANSPLANT PH:

		Mild	Moderate	Total	P value
No	No	4	4	8	0.471
	%	50.0%	50.0%	100.0%	
Yes	No	2	3	5	
	%	33.3%	66.7%	100.0%	
Total	No	6	8	14	
	%	42.9%	57.1%	100.0%	

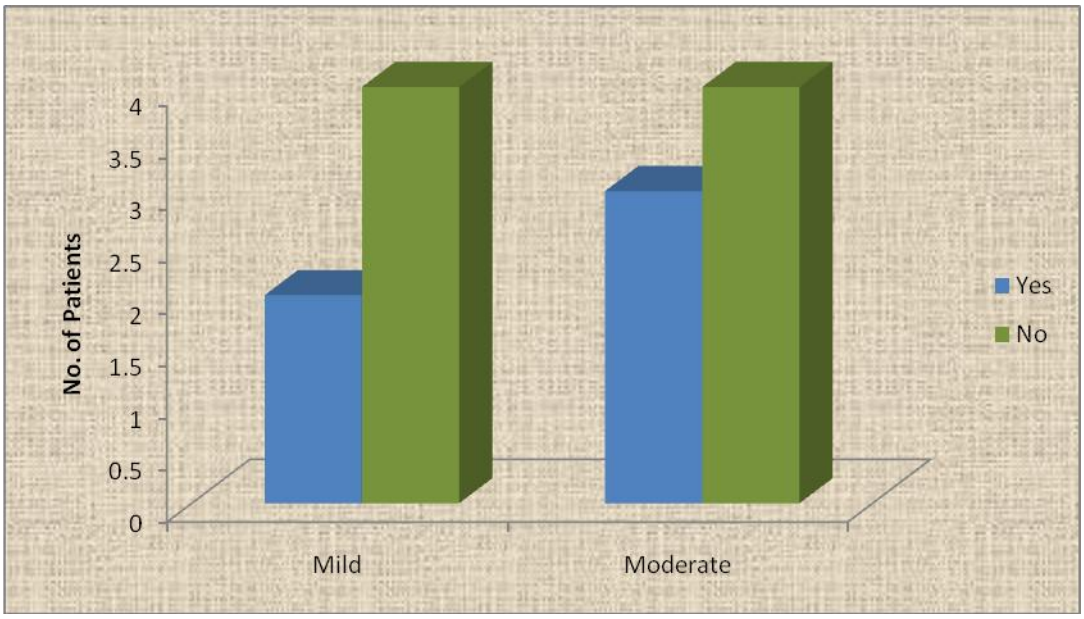


TABLE.12. DIABETES & ESRD IN RELATION WITH AGE PRE TRANSPLANT GROUP

Age		DM			P value
		No	Yes	Total	
<20	No.	2	0	2	0.001
	%	100.0%	0%	100.0%	
21-30	No.	8	0	8	
	%	100.0%	0%	100.0%	
31-40	No.	26	0	26	
	%	100.0%	0%	100.0%	
41-50	No.	7	4	11	
	%	63.6%	36.4%	100.0%	
51-60	No.	2	3	5	
	%	40.0%	60.0%	100.0%	
61-70	No.	1	1	2	
	%	50.0%	50.0%	100.0%	
Total	**No.**	**46**	**8**	**54**	
	%	**85.2%**	**14.8%**	**100.0%**	

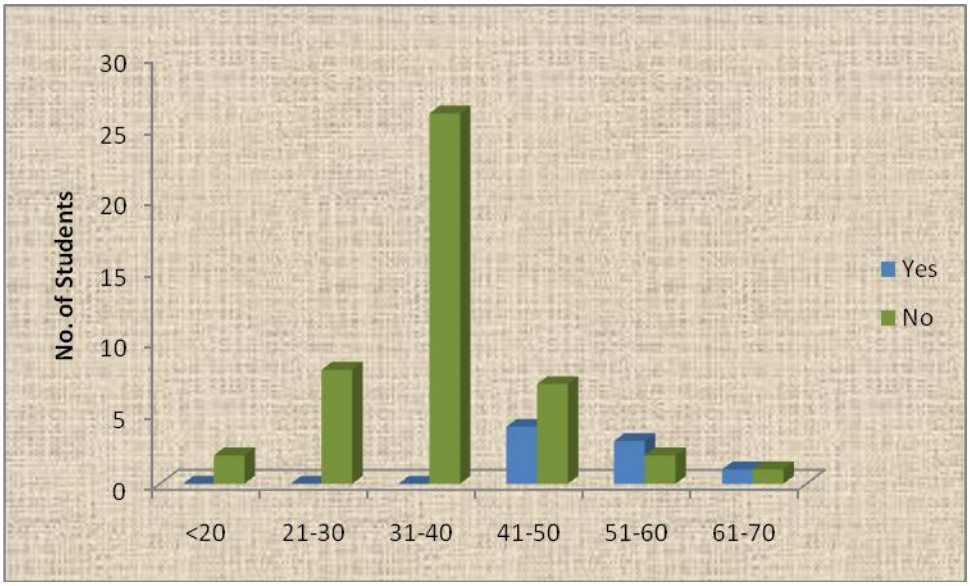
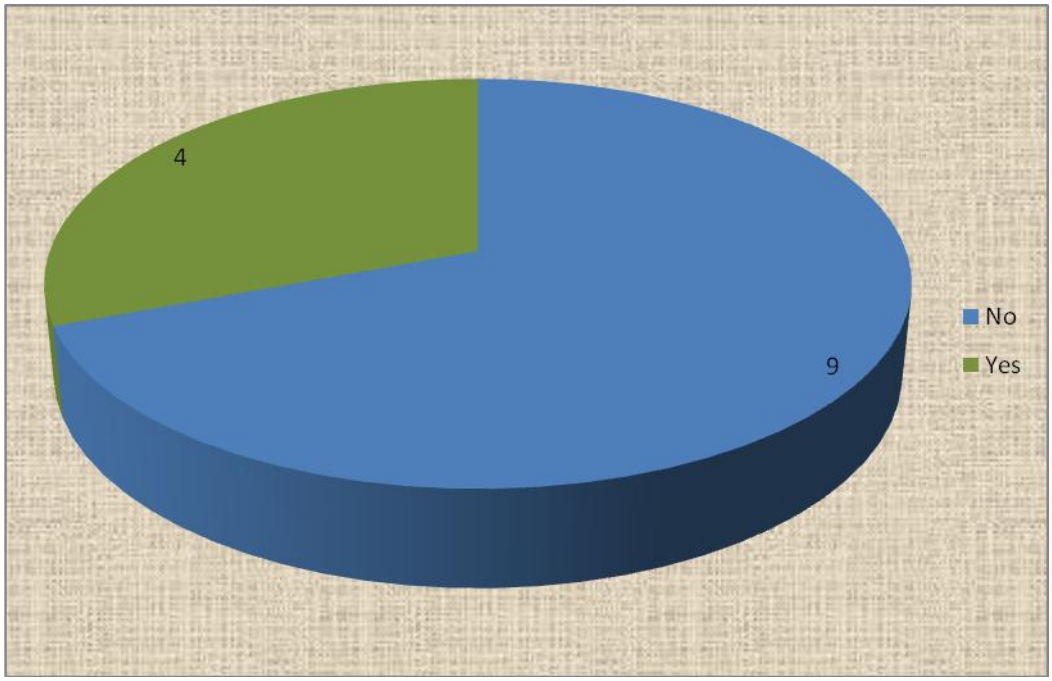


TABLE .13. DIABETIC ESRD WITH PULMONARY HYPERTENSION:

DM with ESRD	No of patients	Percentage (%)
No	9	64.3
Yes	4	35.7
Total	14	100.0



TABLEBLE.14. DM & PRE TRANSPLANT

		Mild	Moderate	Total	P value
No	No	4	5	9	0.657
	%	44.4%	55.6%	100.0%	
Yes	No	2	2	4	
	%	40.0%	60.0%	100.0%	
Total	No	6	7	13	
	%	42.9%	57.1%	100.0%	

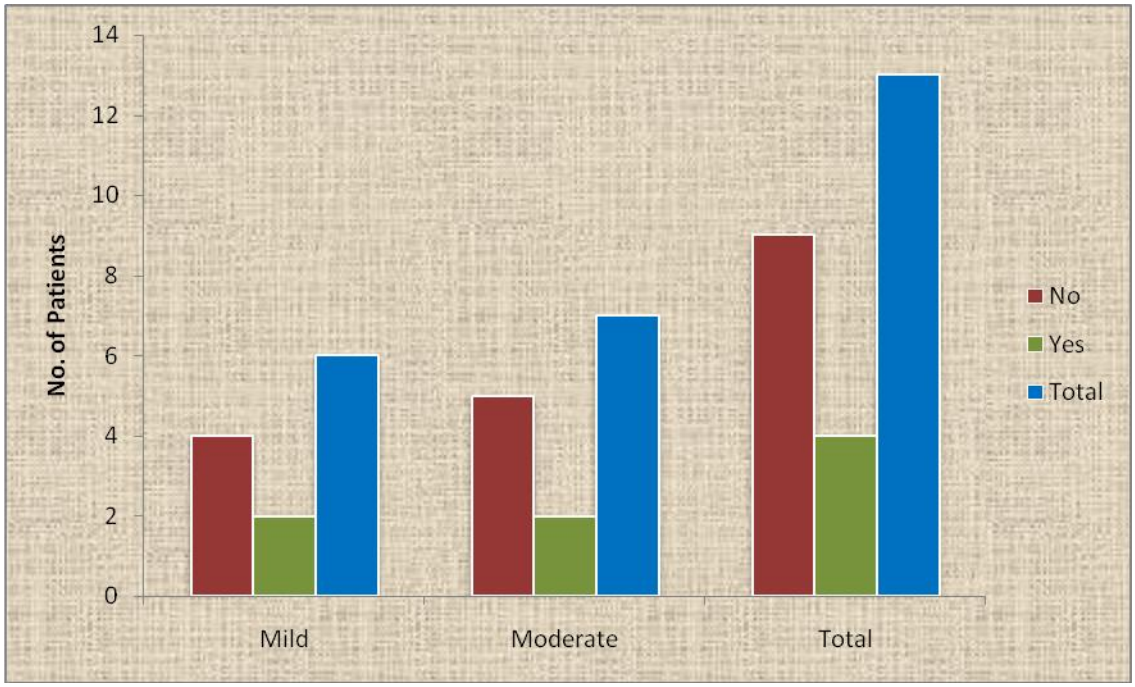


TABLE 15. CORONARY ARTERY DISESAE IN TRANSPLANT POPULATION

CAD	No of patients	Percentage (%)
No	43	78.2
Yes	12	21.8
Total	**55**	**100.0**

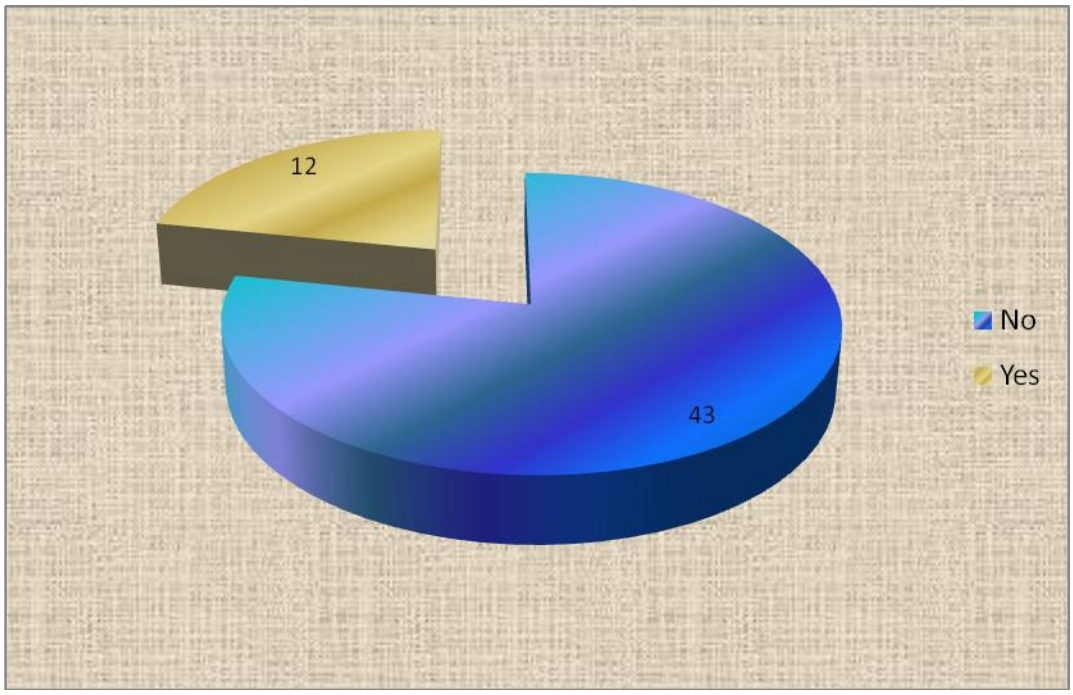


TABLE.16. ESRD WITH CORONARY ARTERY DISEASE AND PH:

CAD	No of patients	Percentage (%)
No	11	84.7
Yes	2	15.3
Total	13	100.0

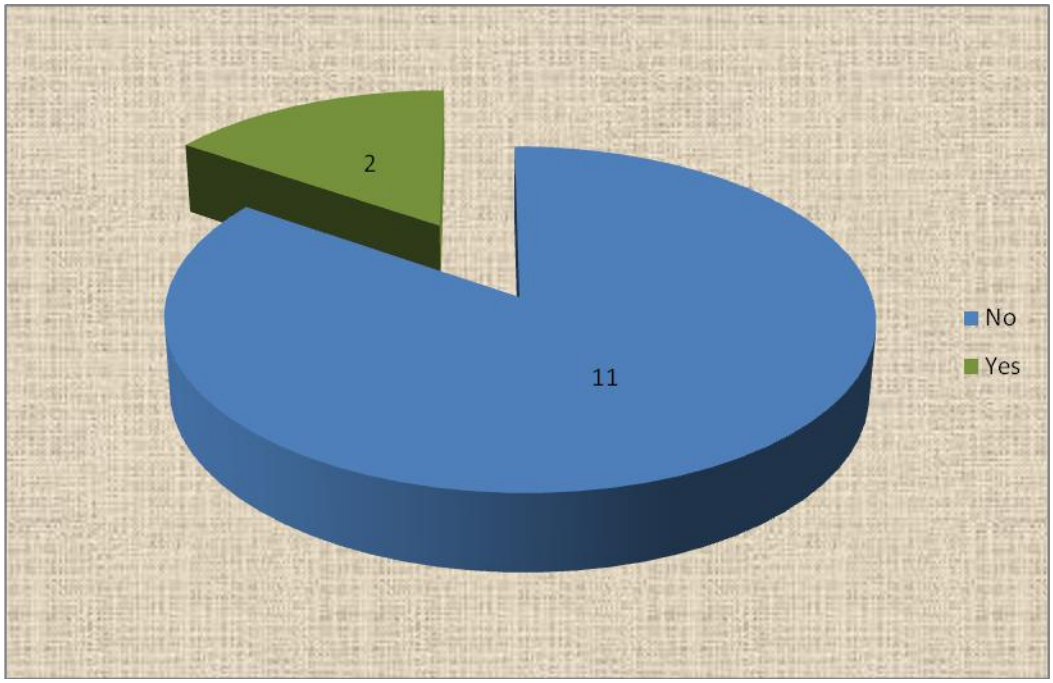


TABLE.17. CAD & PRE TRANSPLANT:

		Mild	Moderate	Total	P value
No	No	6	5	11	0.154
	%	54.5%	45.5%	100.0%	
Yes	No	0	2	2	
	%	.0%	100.0%	100.0%	
Total		6	7	13	
		42.9%	57.1%	100.0%	

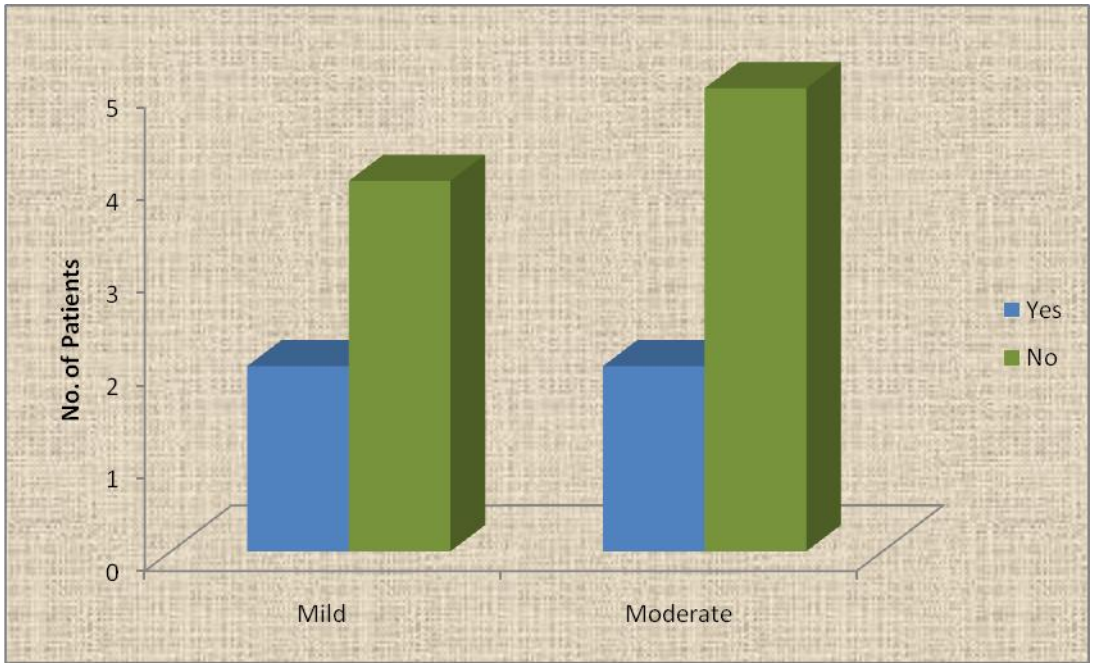


TABLE. 18. PATIENTS WITH MULTIPLE RISK FACTORS AND PH:

Pt. with DM, SHT,CAD	No of patients	Percentage (%)
No	11	78.6
Yes	3	21.4
Total	14	100.0

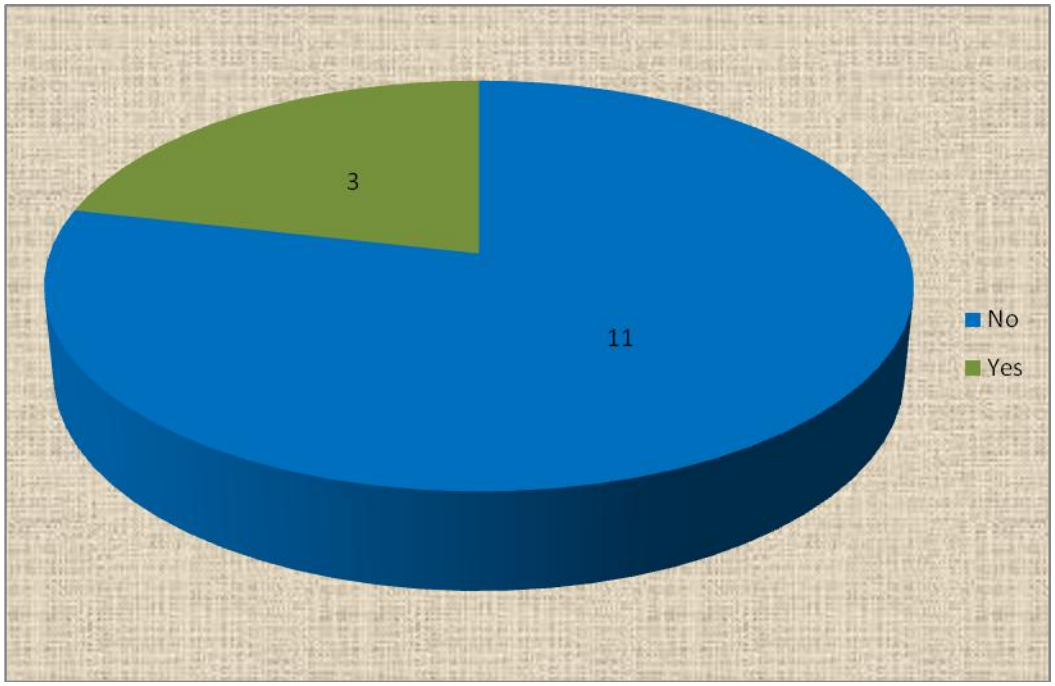


TABLE.19.PATIENT WITH MULTIPLE RISK FACTORS & PRE TRANSPLANT:

		Mild	Moderate	Total	P value
No	**No**	**6**	**5**	**11**	
	%	54.5%	45.5%	100.0%	
Yes	No	0	3	3	**0.154**
	%	.0%	100.0%	100.0%	
Total	No	6	8	14	
	%	42.9%	57.1%	100.0%	

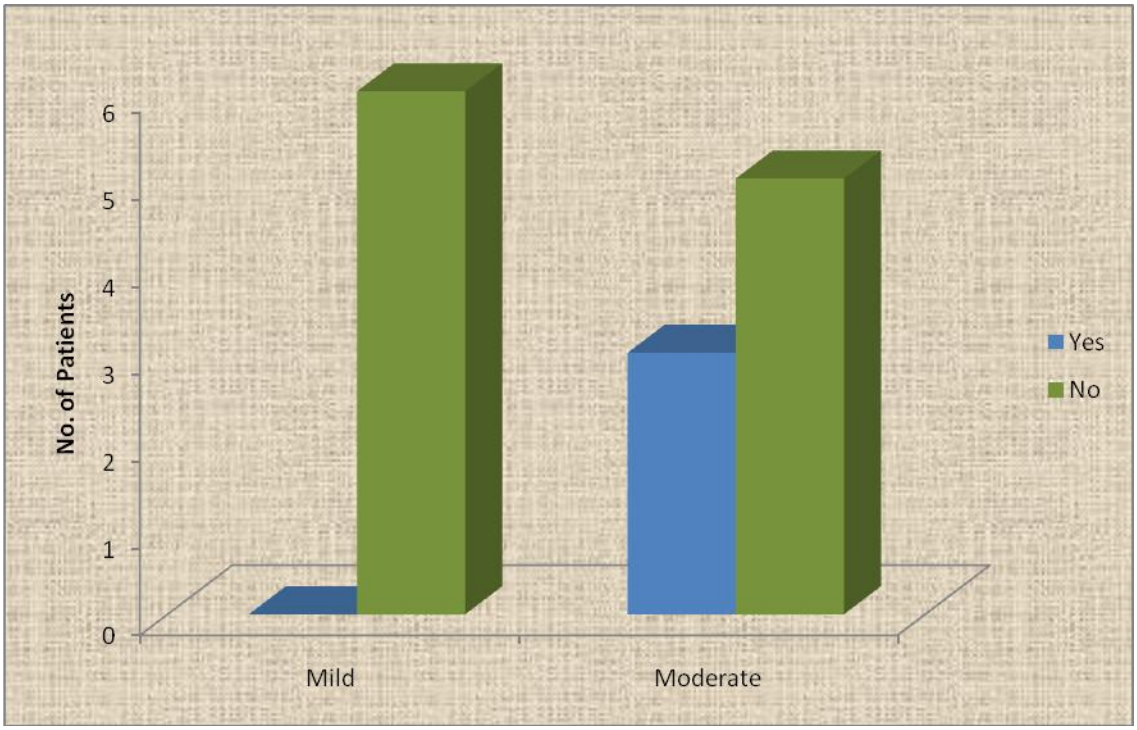


TABLE .20. POST TRANSPLANT AFTER 3&6 MONTHS

		Normal	Mild	Total	P value
No	No	11	0	11	0.003
	%	100.0%	.0%	100.0%	
Yes	No	0	3	3	
	%	.0%	100.0%	100.0%	
Total	No	11	3	14	
	%	78.6%	21.4%	100.0%	

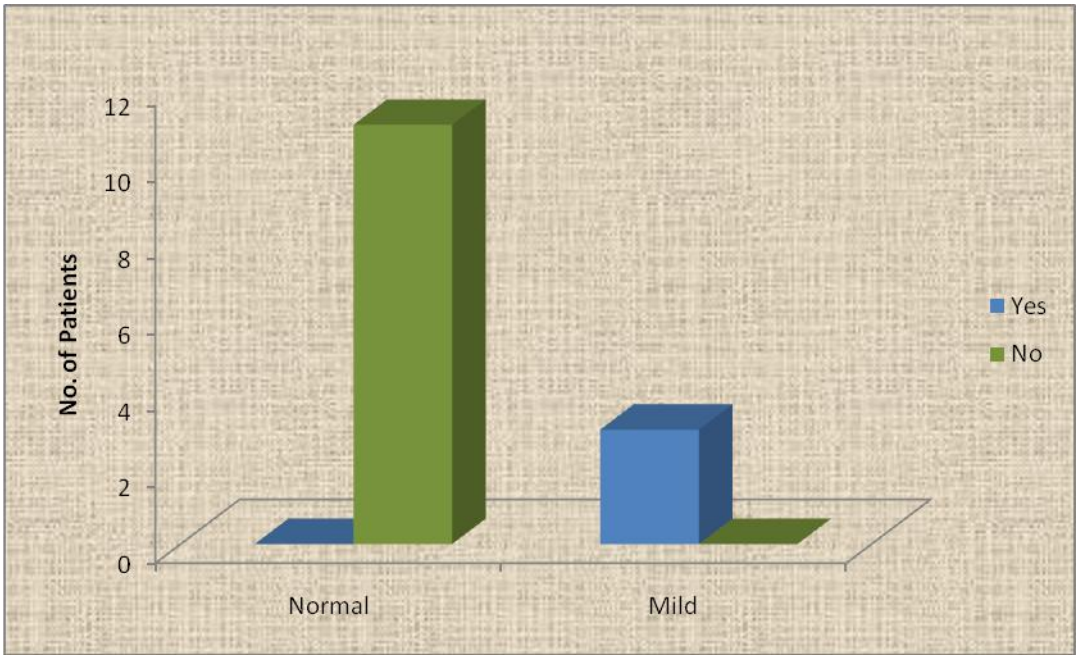


TABLE .21.OUTCOME OF PH IN POST TRANSPLANT 3 MONTHS:

Post transplant after 3 months	No of patients	Percentage (%)
Normal	11	78.6
Mild	3	21.4
Total	**14**	**100.0**

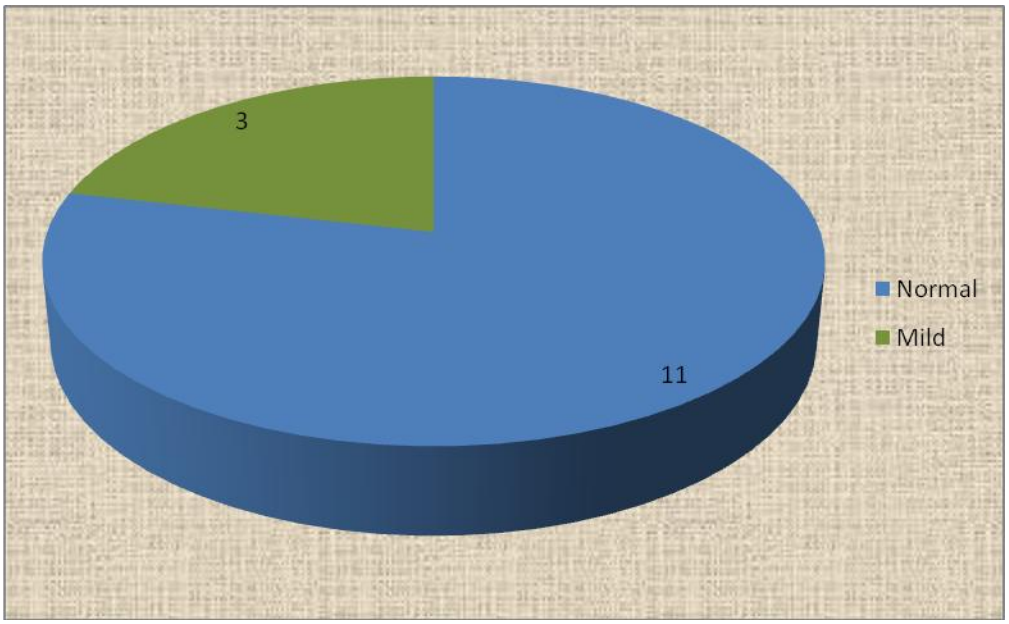
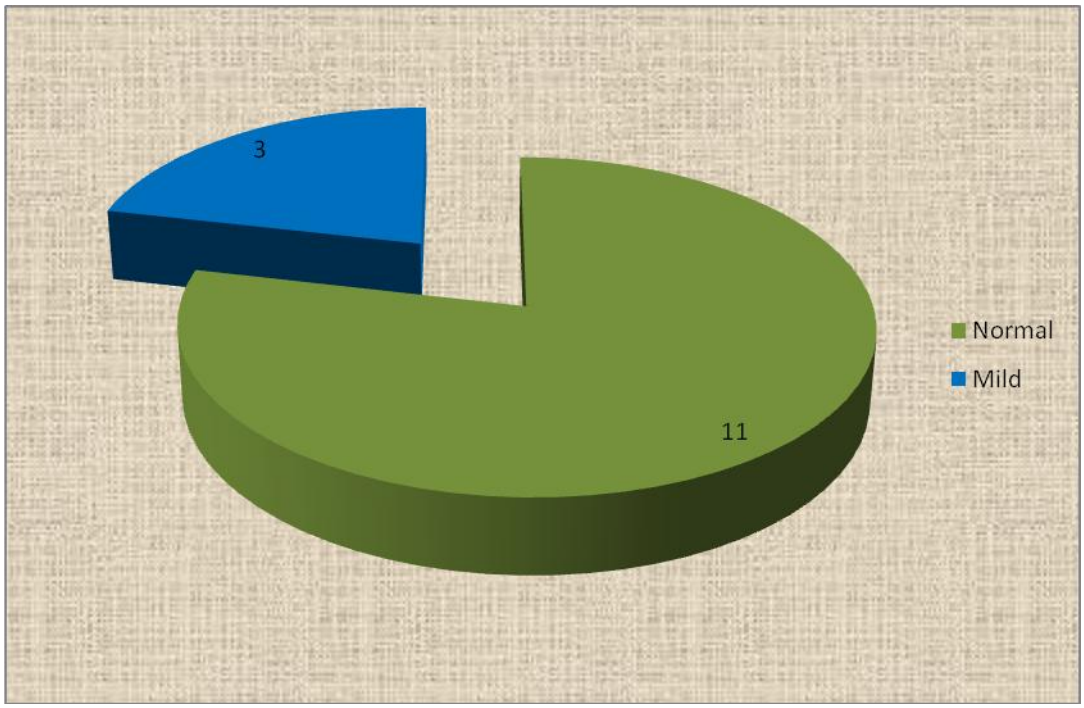


TABLE .22. OUTCOME OF PH IN POST TRANSPLANT 6 MONTHS:

Post transplant after 6 months	No of patients	Percentage (%)
Normal	11	78.6
Mild	3	21.4
Total	14	100.0



DISCUSSION

It's well known fact that in CKD G5D cardiovascular disease is most common cause of mortality which is mostly manifested as LV dysfunction, Ischemic heart disease, or acute Myocardial infarction. The other forms of the cardiovascular disease, other rare manifestations may be pulmonary hypertension[37]. But only limited data is available on pulmonary hypertension in ESRD and Post transplant outcome.

We examined 75 patients out of which 55 cases underwent Renal Transplant in our institute & also fulfilled the inclusion criteria was taken up for the study, 41 patients were excluded by clinical history and examination, laboratory investigation and exclusion criteria [5,7,15,21]. Doppler echocardiography was done in all 55 patients as a part of pre transplant work up and in patient with PH post operatively 3 months and 6 months echocardiography was done. Since it's a non invasive parameter for assessing pulmonary hypertension in this population during monthly OPD follow up.

Among the 55 patients who undergone renal transplantation 22 patients were found to have pulmonary hypertension in the population (40%).

The Distribution age group and sex of the study population[13] was total of 55 patients out of which 31males(41.2%) and 21 females38.1%, and only 2 were of 20 years, 26 were of 31-40 years, 12patients were 41-50 years, 5 patients were 51-60, and pre transplant pulmonary hypertension 'p' value of 0.017.

We compared gender ratio and found that pulmonary hypertension 7 male and 7 female, who fits in our inclusion criteria. As overall population male are more common with 41.2%.and female of 38.1% with 'p' value of 0.524. in pulmonary hypertension group the ration is 1:1.

Most of our cases are live related donor with 76.2% unrelated are 21.8%, and deceased donor of only 1 patient.

We analysed systemic hypertension in our all population who underwent renal transplant showed about 38.2%, with age related most common is 3rd and 4th decade of life with 30.6% and 66.6% and 'p' value of 0.053.

Out of 14 patients (42.9%) Hypertension ESRD, of which 2 had mild pulmonary hypertension, 3 had moderate PH with ‘p’ value of 0.471.

Among the pre transplant group we found 8 cases (40%) having DM, when compared to age relation compared 36.4% aged from 41-50, and only 3 were from 51-60. PH with ‘p’ value of 0.001.

In association with pulmonary hypertension and Diabetic ESRD we found only 4 patients, 2 patients with mild PH, 2 with moderate PH. calculating a ‘p’ value of 0.657.

In our study group we found 12cases to have coronary artery disease and ESRD 21.8%outof 55 patients, with pulmonary artery hypertension 2 had moderate PH (45.4%) ‘ p’ value of 0.154.

We also analysed the data and found 3 patients (21.4%) had multiple risk factors like SHT, DM.CAD& ESRD in the study group of 14 patients (78.4%) ‘P’ value of 0.154.

In total of pre transplant workup with pulmonary Hypertension we had 14 patients with mild and moderate PH, 8 cases Severe PH were not included in this study due to exclusion criteria.

Out of 55 patients who received renal transplant 22 had pulmonary hypertension of which 14 patients were included for analysis.

Out of 14 patients 5had Hypertension and ESRD of which 2 had mild PH and 3 had moderate PH, 4 patients had diabetes and ESRD of which 2 had mild PH, 2 had moderate PH, 2 patients had coronary artery disease and ESRD both had moderate PH.

3 patients had SHT, DM, CAD & ESRD. All 3 had moderate PH.

Mild and moderate PH in Hypertensive ESRD, Diabetic ESRD, Coronary artery disease & ESRD, became normal 3 and 6 month post transplant.

The moderate PH in the hypertension, Diabetic, Coronary artery disease & ESRD, group became mild PH in post Transplant 3and 6 months.

There was a significant favourable outcome in patients who underwent Renal Transplant when followed up (with echocardiography)[3,5,7] after first 3 months of transplant showed a ‘p’ value of 0.002. And follow up after 6moths duration showed a good prognosis improved to mild PH showed a ‘p’ value of 0.008. Serife savas et. al.,

concluded that patients have PH with ESRD has benefited by renal transplantation.

Till date only one study on pulmonary hypertension in post renal transplantation with Doppler echocardiography was done by Issa et al reported pulmonary hypertension in ESRD group of patient's Doppler echocardiography was done as a part of workup. David et al., showed that Non-invasive detection of pulmonary hypertension prior to renal transplantation is a predictor of increased risk for early graft dysfunction.

LIMITATIONS

- The major limitations of this study are small sample size.
- Observational study
- Echocardiography which has subjective variation, used as a parameter.
- Cases of Severe Pulmonary hypertension are excluded because they are not fit for renal transplant.
- Right sided cardiac catheterization and Doppler echocardiography were not performed simultaneously.

SUMMARY AND CONCLUSION

- 14 patients with pulmonary hypertension and ESRD who has undergone renal transplant were followed up in the post transplant period. PH became normal in 11 patients during 3^{rd} and 6^{th} month. Of these 11 patients 5 had Hypertension and ESRD, 4 had Diabetic and ESRD, 2 had Coronary artery disease and ESRD.
- In the remaining 3 patients moderate PH in the pre transplant period regressed to mild PH on follow up. All the 3 co-morbid factors (DM, SHT, CAD), were present in this sub- group which may be the reason for incomplete resolution of PH.
- Renal transplant offers a significant resolution of PH in all sub groups in post transplant period.

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ANNEXURE-I

LIST OF ABBREVIATIONS USED

PAH	:	Pulmonary Arteial Hypertension
PH	:	Pulmonary Hypertension
CKD	:	Chronic Kidney Disease
CAD	:	Coronary Artery Disease
DM	:	Diabetes Mellitus
SHT	:	Hypertension
CVD	:	Cardio Vascular Disease
ECG	:	Electro Cardiogram
CHD	:	Coronary Heart Disease
COPD	:	Chronic Obstructive Pulmonary Disease
HIV	:	Human Immunodeficiency Virus
WHO	:	World Health Organization
NO	:	Nitric Oxide
ADMA	:	Asymmetric Dimethylarginine

ANNEXURE-II

CASE PROFORMA

Name: Age: Sex:

IP No: OP No:

Diagnosis: Native Kidney Disease:

Causes of renal failure:

Duration of temp catheter:

Duration of AVF:

Risk Factors: DM / SHT / Smoker / Family History

General examination:

BP:

PR:

SPO2:

HR:

CVS:

RS:

P /A:

CNS:

Pre transplant work up & Echocardiography

Renal transplant date:

Pre transplant out come:

Echocardiography in first 3 months:

Echocardiography in first 6 months:

PSG Institute of Medical Sciences & Research
Institutional Human Ethics Committee

POST BOX NO. 1674, PEELAMEDU, COIMBATORE 641 004, TAMIL NADU, INDIA
Phone : 91 422 - 2598822, 2570170, Fax : 91 422 - 2594400, Email : psgethics2005@yahoo.co.in

June 24, 2013

To
Dr N Siva
DM Postgraduate
Department of Nephrology
PSG IMS & R
Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on June 21, 2013 in its expedited review meeting held at College Council Room, PSG IMS&R, between 2.00 pm and 3.30 pm, and discussed your application to conduct the study entitled:

"Outcome of pulmonary hypertension in post renal transplant recipient"

The following are the suggestions / recommendations made by the members:

- Please provide justification for sample size
- Please include Informed Consent Form in Tamil

Please clarify.

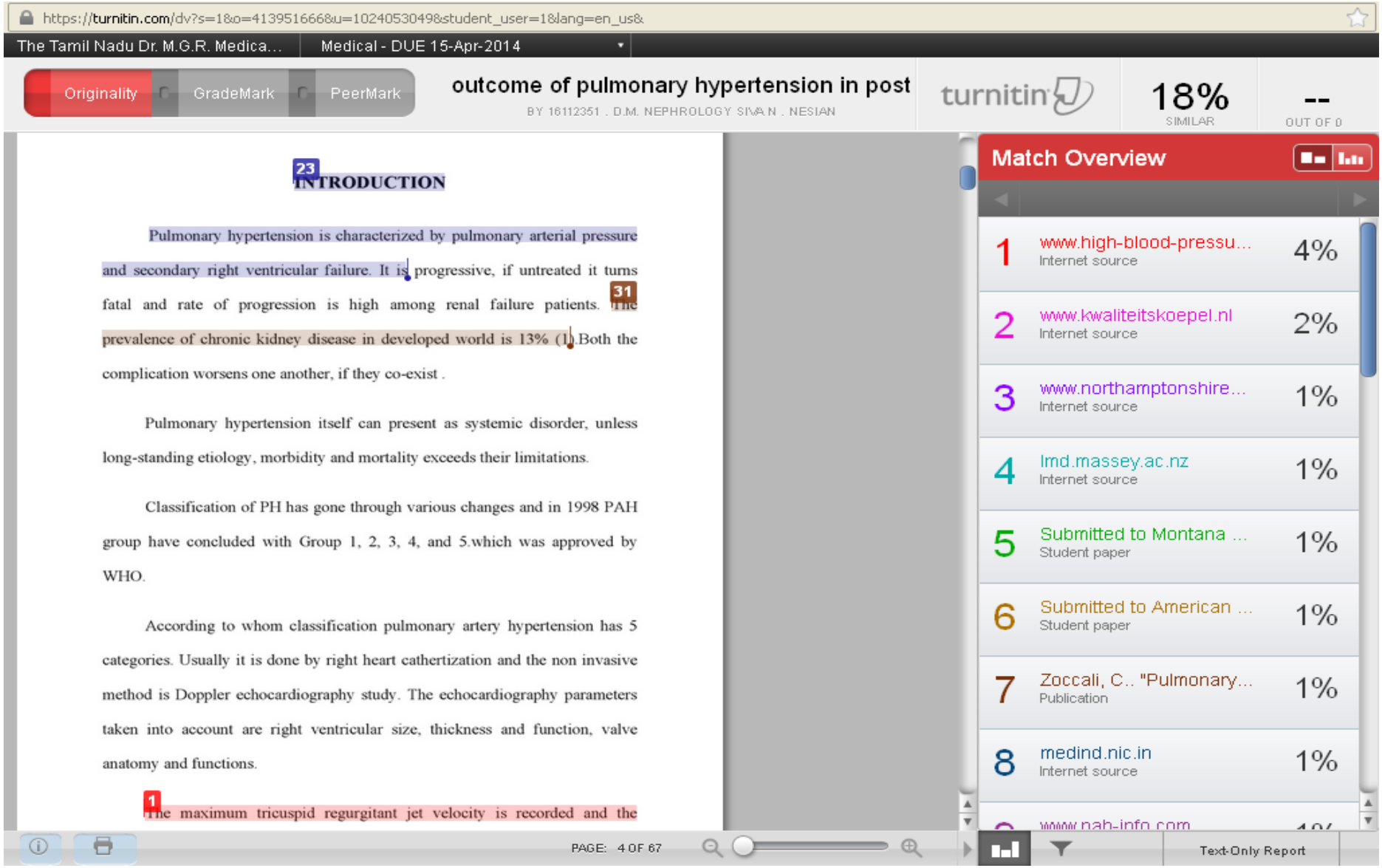
Decision: Approval subject to the verification of the above mentioned documents / modifications by IHEC.

Yours truly,

26.6.13

Dr S Bhuvaneshwari
Member - Secretary
Institutional Human Ethics Committee

SECRETARY
PSG IMS & R
COIMBATORE-641 004
INSTITUTIONAL HUMAN ETHICS COMMITTEE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INTRODUCTION
Pulmonary hypertension is characterized by pulmonary arterial pressure and secondary right ventricular failure. It is progressive, if untreated it turns fatal and rate of progression is high among renal failure patients. The prevalence of chronic kidney disease in developed world is 13% (1).Both the complication worsens one another, if they co-exist .
Pulmonary hypertension itself can present as systemic disorder, unless long-standing etiology, morbidity and mortality exceeds their limitations.
Classification of PH has gone through various changes and in 1998 PAH group have concluded with Group 1, 2, 3, 4, and 5.which was approved by WHO.
According to whom classification pulmonary artery hypertension has 5 categories. Usually it is done by right heart cathertization and the non invasive method is Doppler echocardiography study. The echocardiography parameters taken into account are right ventricular size, thickness and function, valve anatomy and functions.
The maximum tricuspid regurgitant jet velocity is recorded and the
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ABSTRACT

Introduction