"SUBCLINICAL CARDIAC ABNORMALITIES IN VARIOUS STAGES OF CHRONIC KIDNEY DISEASE"

By

DR. S. DWARAK

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

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IN

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Under the Guidance of

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SRI DEVARAJ URS MEDICAL COLLEGE,

TAMAKA, KOLAR – 563 101

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Date: **Dr.S.DWARAK**

Place: Kolar

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LIST OF ABBREVIATIONS USED

2D ECHO	2-Dimensional Echocardiogram
ACEi	Angiotensin Converting Enzyme Inhibitor
ARBs	Angiotensin Receptor Blockers
ADMA	Asymmetric Di-Methyl-Arginine
AGEs	Advanced Glycation End Products
AVF	Arterio-Venous Fistula
BMI	Body Mass Index
CAD	Coronary Artery Disease
CCF	Congestive Cardiac Failure
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CMRI	Cardiac Magnetic Resonance Imaging
CRP	C-Reactive Protein
CRS	Cardio-Renal Syndrome
cTn	Cardiac Troponin
cTn-I	Cardiac Troponin I
cTn-T	Cardiac Troponin T
CVD	Cardiovascular Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration

CRIC study	Chronic Renal Insufficiency Cohort study
DM	Diabetes Mellitus
E/A	Peak Early Diastolic Velocity / Peak Atrial filling Velocity
ECG	Electro-Cardio Gram
ESR	Erythrocyte Sedimentation Rate
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
FGF -23	Fibroblast growth factor-23
HF	Heart Failure
HD	Haemodialysis
HDL	High Density Lipo-Proteins
HTN	Hypertension
IHD	Ischemic Heart Disease
IVS	Interventricular Septum
KDIGO	Kidney Disease Improving Global Outcome
LDL	Low Density Lipo-Proteins
LV	Left Ventricle
LVH	Left Ventricular Hypertrophy
MMRC	Modified Medical Research Centre

MRI	Magnetic Resonance Imaging
MPS	Myocardial Perfusion Scintigraphy
NKF	National Kidney Foundation
NOS	Nitric Oxide Synthase
PAH	Pulmonary Artery Hypertension
LVPWd	Left Ventricular Posterior Wall Thickness(diastole)
LVPWs	Left Ventricular Posterior Wall Thickness(Systole)
RAAS	Renin-Angiotensin-Aldosterone System
R-AGE	Receptor for Advanced Glycation End Products
RRT	Renal Replacement Therapy
RWMA	Regional Wall Motion Abnormality
SPECT	Single-Photon Emission Computed Tomography
SPAP	Systolic Pulmonary Artery Pressure
VLDL	Very Low Density Lipoproteins

Abstract

Title: "Study of Subclinical Cardiac Abnormalities in CKD Patients"

Background:

Chronic Kidney Disease (CKD), a global health burden estimated to affect up to 15% of adult populations, has been identified as an important predisposing factor for the development of Cardiovascular disease, and it also portends an increased risk of mortality and morbidity[1]. Cardiovascular disease (CVD) and kidney disease are closely interrelated and disease of one organ causes dysfunction of the other, ultimately leading to the failure of both organs.

Among patients without clinical heart failure, the associations at different stages of eGFR with changes in cardiac structure and function are not well described in literature. Not many research studies have described the associations of different stages of estimated GFR (eGFR) with the range of changes in cardiac structure and function in patients with established CKD [4]. This study hypothesizes that subclinical cardiac changes start in the early stages of CKD and that this association strengthens with more advanced kidney disease.

In addition, the severity and extent of cardiovascular abnormalities in CKD patients is disproportionate to the number and severity of traditional risk factors. The relative significance of non-traditional risk factors for CVD such as anemia, uremia, calcium and phosphate metabolism disorders in CKD are not well defined. It would be informative to detect subclinical cardiac abnormalities in various stages of CKD and its correlation with various non traditional risk factors so that a multipronged approach can be formulated to prevent occurrence of cardiovascular events in this high risk population.

Objectives:

1. To detect Echocardiographic evidence of cardiac abnormalities in various stages of CKD
2. To classify the subclinical heart failure into Systolic and Diastolic forms
3. To correlate cardiovascular abnormalities with non traditional cardiovascular risk factors (Anemia, Proteinuria and Calcium and Phosphorous metabolic abnormalities and inflammation(increased ESR))

Materials and Methods:

This study was conducted on 64 patients diagnosed with Chronic Kidney Disease with no clinical features of heart failure attending the General Medicine outpatient section and inpatients of R.L.Jalappa Hospital and Research Centre Tamaka, Kolar.

Inclusion Criteria:

- Age Between 18 to 60 years
- Patients with established CKD as defined by CKD-EPI formula (< 60 ml/min/1.73 m^2) of more than 3 months associated with elevated serum creatinine and with or without albuminuria and with or without structural changes determined by Ultrasonography with no features of Congestive cardiac failure.

Exclusion criteria:

- Prior transplantation
- Acute Kidney Injury
- Systemic or hematogenous malignancy
- Rheumatic Heart Disease & Congenital heart Disease
- Pre-existing cardiovascular disease like myocarditis due to infective aetiology, primary heart muscle diseasesolike cardiomyopathies
- Severe comorbid illnesses, such as cirrhosis, HIV disease, and severe (New York Heart Association class III or IV) Heart Failure and COPD (MMRC grade III or IV)

Methods of Collection of Data:

This study was conducted on patients attending the general medicine outpatient section and inpatient of R.L.Jalappa Hospital and Research Centre Tamaka, Kolar. Consecutive patients, diagnosed to have CKD who satisfy the inclusion and exclusion criteria were enrolled in the study after obtaining informed consent. A detailed history with regard to cardiac symptoms such as dyspnea, orthopnea , chest pain and palpitations was recorded. Physical examination was carried out to detect signs of cardiac failure and hypertension.

16 cases each of Stage 1 &2, 3, 4 and 5 based on eGFR were included in the final analysis adding up to a total of 64 will form the study group.

Laboratory investigations to detect elevated urea, creatinine, anemia, calcium and phosphorous metabolic abnormalities, proteinuria and dyslipidemia was undertaken. USG of Kidneys was done to measure the Renal size.

Participants was subjected to Chest X-Ray, ECG and Echocardiogram to detect pericardial, myocardial and endocardial changes.

2D–Transthoracic Echocardiography machine was used with 3.5 MHz transducer probe and Two dimensional echocardiography and M- mode echocardiography were subsequently done on the subjects. The LVEF was taken as measure of left ventricular systolic function. Diastolic function was determined by measuring E/A ratio by special Doppler inflow velocity. LVH and LV Mass Index were also measured.

RESULTS:

We performed a Prospective Observational study of various traditional and non-traditional cardiovascular risk factors in CKD and their impact on echocardiographic measurements of cardiac function.

The mean age of our cohort was 46 years ± 5 years. 60% of the patients were below the age of 60 years whereas 40% were above the age of 60 years. Men constituted 63% of the study population while females constituted 27%. The mean Body Mass Index was 22 ± 2.4.

56% of the patients were diabetics and 76% were hypertensives. 36% were smokers and 25% consumed alcohol regularly. 54% of patients had low Haemoglobin levels below 11 %. Only 14% were having hypercholesterolemia highlighting reverse causality of low cholesterol levels with higher cardiovascular mortality in late stages of CKD.

Only 1.5 % of patients were shown to have high LDL levels above 125 mg /d L again pointing towards the role of malnutrition in cardiovascular pathogenesis.

65% of the patients were having low HDL levels. Serum albumin levels were less than 3g/dL in 60% of patients with Protein Energy Wasting and higher risk of CV morbidity and mortality. 22% were with Nephrotic range proteinuria which is another major non- traditional risk factor. Diastolic dysfunction was a major subclinical Echocardiographic finding in 31% of Stage I CKD and 100% of Stage V CKD. Systolic dysfunction was seen in 18% of CKD Stage I patients and 37% of Stage V CKD patients. LVH was seen in 71 % of patients constituting a heavy burden of cardiovascular disease in this cohort.

Traditional risk factors such as High systolic BP, Diabetic status and Smoking status had positive association with LVH.

Non-traditional risk factors such as Estimated GFR, ESR, Anaemia, Albuminuria, Hyperphosphatemia, Hypocalcemia and Metabolic acidosis were shown to be significantly associated with Left Ventricular Mass Index by Univariate analysis.

In Multivariate analysis, it was shown that Estimated GFR and Hyperphosphatemia were significant predictors of Left ventricular Mass Index.

CONCLUSION:

It has been observed that subclinical echocardiographic abnormalities are common in CKD patients. Both traditional and many potentially modifiable Non-traditional risk factors have shown significant correlation with several Echocardiographic abnormalities.

In our study we found that Hypertension, Anemia, Estimated GFR, Serum calcium, Phosphorus levels and Albuminuria were such factors. These have to be addressed at multiple levels by Blood Pressure Control, Iron and Erythropoietin therapy for anemia, Phosphate restriction and Phosphate binders and lastly reducing the Inflammatory status of High CRP levels by improving nutritional status . It can be concluded that the cardiovascular Prognosis can be considerably improved if such multi-pronged approach is undertaken to address the risk factors from an early stage of CKD.

INTRODUCTION

Chronic Kidney Disease (CKD), a global health burden estimated to affect up to 15% of adult populations, defined by either kidney damage or an elevated creatinine or an estimated GFR (eGFR) <60 ml/min per 1.73 m^2 for greater than three months has been identified as an important predisposing factor for the development of Cardiovascular disease, and it also portends an increased risk of mortality and morbidity[1]. One of the biggest challenges in current clinical nephrology is to bring down the exponential rise of cardiovascular comorbidity in CKD patients. Cardiovascular disease (CVD) and kidney disease are closely interrelated and disease of one organ cause dysfunction of the other, ultimately leading to the failure of both organs. Patients with end-stage renal disease (ESRD) are at an increased risk of mortality due to CVD as compared to ESRD itself.

Patients with Chronic Kidney Disease suffer from an increased risk of cardiovascular abnormalities like Heart Failure, Myocardial infarction, Arrhythmias, valvular lesions and sudden cardiac death[1]. Abnormal left ventricular geometry and functions are common in this patient group and have been proven to be linked with increased cardiovascular mortality/morbidity and all-cause mortality in this population.

Clinical cardiac failure has been shown to be independently associated with development of renal disease and this complex interdependence of heart and kidney function is referred to as the cardiorenal syndrome. Many patients with Chronic Kidney Disease die prematurely before initiation of dialysis due to adverse cardiovascular events[1].

Several studies have evaluated associations between kidney function and abnormal left ventricular geometry in patients with advanced disease, and in those requiring dialysis[2] and there have been some studies looking at associations even in earlier stages, in addition to diastolic dysfunction and CKD[3]. In CKD patients diastolic dysfunction of the left ventricle occurs frequently and is linked with the occurrence of heart failure (HF) and higher mortality[4].

Other studies had demonstrated that CKD severity was the most independent predictor of elevated LV filling pressures and could be responsible for impaired systolic and diastolic functions in pre-dialysis CKD[3]. Among patients without clinical heart failure, the associations at different stages of eGFR with changes in cardiac structure and function are not well described in literature. Not many research studies have described the associations of different stages of estimated GFR (eGFR) with the range of changes in cardiac structure and function in patients with established CKD [4]. This study hypothesizes that subclinical cardiac changes start in the early stages of CKD and that this association strengthens with more advanced kidney disease.

Although a huge number of patients with CKD have traditional cardiac risk factors such as diabetes, hypertension and abnormalities in cholesterol, interventions to address these factors--which have significantly decreased cardiovascular mortality in the general population--have not shown such benefit in the CKD population.

In addition, the severity and extent of cardiovascular abnormalities in CKD patients is disproportionate to the number and severity of traditional risk factors. This realization has focused attention on nontraditional cardiac risk factors that are particularly relevant to patients with CKD, including decreased hemoglobin levels, microalbuminuria, increased inflammation and oxidative stress, and abnormalities in bone and mineral metabolism. The relative significance of non-traditional risk factors

for CVD like anemia, uremia, calcium and phosphate metabolism disorders in CKD are not well defined. However, toxins resulting from uraemia and renal dysfunction play a significant role in the development CVD[5]

Recognizing that factor is very important, because prevention of CV death is achieved not only by delaying the progression of CKD, but also by modifying CV risk factors early in the course of the disease. It would be informative to detect subclinical cardiac abnormalities in various stages of CKD and its correlation with various non-traditional risk factors so that a multipronged approach can be formulated to prevent occurrence of cardiovascular events in this high risk population.

OBJECTIVES:

1. To detect echocardiographic evidence of cardiac abnormalities in various stages of CKD

2. To classify the subclinical heart failure into Systolic and Diastolic forms

3. To correlate cardiovascular abnormalities with non-traditional cardiovascular risk factors (Anemia, Proteinuria and Calcium and Phosphorous metabolic abnormalities and inflammation (increased ESR)

REVIEW OF LITERATURE

CHRONIC KIDNEY DISEASE: DEFINITION AND INTRODUCTION

Chronic kidney disease (CKD) incorporates numerous pathophysiologic processes linked to aberrant renal function and a progressive decline in glomerular filtration rate (GFR). The classification of CKD has recently been updated, in which stages of CKD are stratified by both estimated GFR and the amount of albuminuria, in order to predict risk of progression of CKD. In the past, CKD had been staged only by taking GFR into consideration[6]. However, the risk of advancing chronic kidney disease through various stages is closely associated with the degree of albuminuria, and hence this has been incorporated into the classification[7].

Stages 1 and 2 CKD are generally not associated with any symptoms arising from the decrement in GFR. If the decline in GFR progresses to stages 3 and 4, clinical and laboratory complications of CKD become more apparent. Virtually all organ systems are affected, but the most evident complications include anaemia and associated easy fatigability; decreased appetite with progressive malnutrition; abnormalities in calcium, phosphorus, and mineral-regulating hormones, and abnormalities in sodium, potassium, water, and acid – base homeostasis[8].

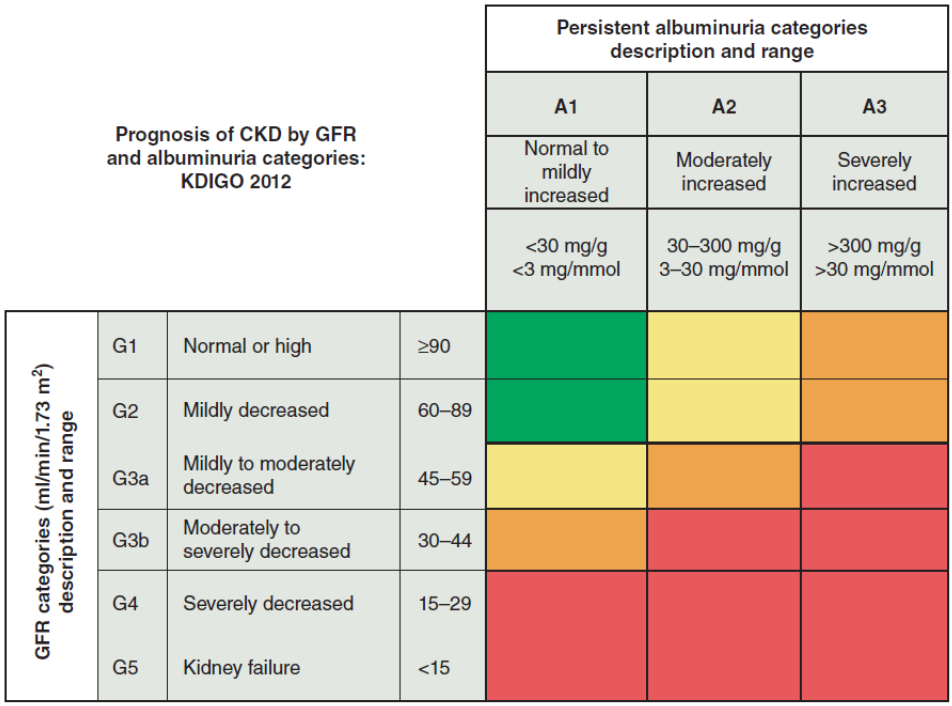


Figure 1:"Kidney Disease Improving Global Outcome (KDIGO) - classification of chronic kidney disease (CKD)". Gradation of color from green to red corresponds to increasing risk and progression of CKD. GFR, glomerular filtration rate. *(Reproduced from Kidney Int Suppl 3:5-14, 2013.)*

Table 1: Estimated Glomerular Filtration Rate (GFR)

Recommended Equations for Estimation of Glomerular Filtration Rate (GFR) Using Serum Creatinine Concentration (SCr), Age, Sex, Race, and Body Weight

1. Equation from the Modification of Diet in Renal Disease study

Estimated GFR (mL/min per 1.73 m2) = 1.86 × (SCr) −1.154 × (age)−0.203

Multiply by 0.742 for women

Multiply by 1.21 for African ancestry

2. CKD-EPI equation

$GFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$

Multiply by 1.018 for women

Multiply by 1.159 for African ancestry

where SCr is serum creatinine in mg/dL, 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 SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.

CHRONIC KIDNEY DISEASE: A PUBLIC HEALTH PROBLEM

The occurrence and prevalence of chronic kidney disease (CKD) has reached considerable proportions warranting it to be called a "public health burden", as a large number of patients are being diagnosed with the condition and it lays a huge economic burden on the patients. Worldwide, Chronic Kidney Disease is the 12th most common cause of death and the 17th most common cause of disability, respectively. This might be an underestimate as many patients with Chronic Kidney Disease are more likely to die of cardiovascular disease (CVD) than to reach end-stage renal disease (ESRD). With an exponentially increasing number of patients being diagnosed with diabetes mellitus (DM) and an aging population, approximately 30% of patients with diabetes mellitus (DM) have been reported to have diabetic nephropathy and as a result there is a concurrent increase in the in incidence of CKD[9].

With increasing prevalence of CKD, CKD related excess CVD, ESRD and the consequent financial burden of renal replacement therapy (RRT), the magnitude of the burden of CKD and its risk factors has to be realized. The prevalence of ESRD and patients on RRT has increased over last two decades[10]. In community-based studies, the CKD prevalence has been variously reported between 0.16% and 0.79%. It has to be taken in to account that the actual prevalence of CKD is much higher than the reported number studies intended to detect CKD stage 3 and above[11-12]. The incidence of ESRD has been observed to be 160–232 per million population (pmp)[13,14] and the projected ESRD prevalence was 785–870 pmp.[15,16]

The Indian CKD Registry, a voluntary reporting body of CKD patients data, initiated in June 2005, has 199 contributing centres. The database has 63,538 patients enrolled, 70% of them males and 73.6% of them have CKD stage 4 and 5. Diabetes is

the cause of kidney disease in 30% of these patients. In summary, the yearly incidence of ESRD in India is approximately 150–200 pmp and DM is an important cause of CKD in approximately 30–40% of the patients. Patients with CKD are likely to die of CVD than to reach ESRD [17].

CKD and CVD: THE MAGNITUDE OF BURDEN

Patients on dialysis have a 10- to 30-fold increased risk for cardiovascular mortality compared with the general population. CVD is the number one cause of death among patients receiving long-term dialysis; accounting for 44% of overall mortality[18]. Patients with ESRD have started surviving longer on maintenance haemodialysis and hence the magnitude of the disease burden has become more apparent.

Furthermore patients with a reduced glomerular filtration rate (GFR) are more likely to die of CVD even before they are to develop ESRD. Heart failure accounts for 15%, myocardial infarction for about 10% and pericarditis for about 3% of dialysis associated mortality [19]. Sudden cardiac death might be linked to the increased prevalence of left ventricular dysfunction secondary to the LVH in dialysis patients[19].
It has been reported that as compared to non-CKD patients, where CVD prevalence is about 13.9% in men and 9.3% in women, the prevalence of CVD among stage 1-5 non-dialysis CKD patients is 17.9% and 20.4%, respectively for men and women. This rate goes up to 40% in dialysis patients and at this stage close to 85% of the patients have been reported to have abnormal left ventricular function or structure, as per echocardiographic criteria[20,21]

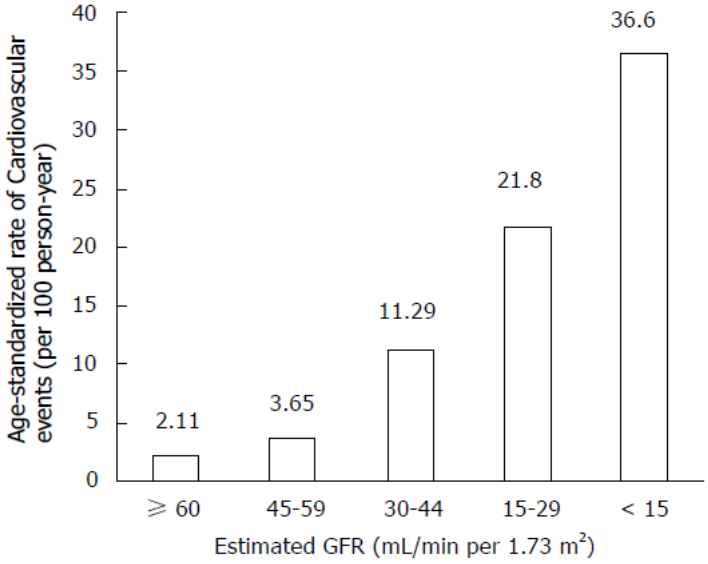


Figure 2: Cardiovascular event rates based on various stages of chronic kidney disease[22]

LVH when measured by nuclear magnetic resonance (NMR) imaging has a 12% prevalence in stage 2 CKD patients[22].The prevalence in stage 3–5 CKD varies from 27% to 74%[23,24] a phenomenon depending on differences in background risk factors and comorbidities. The study reporting the lowest LVH prevalence (27%) included patients with an average age of 50 years and with no evidence of peripheral vascular, cerebrovascular, valvular heart disease, or coronary artery disease and with satisfactory compliance to antihypertensive drugs medications[26]. The research study with the highest prevalence (74%) focused on a series of non-diabetic patients with an average age of 63 years and excluded only patients with very severe ischaemic heart disease[27]

Out of 3487 participants of the Chronic Renal Insufficiency Cohort (CRIC) Study[28] one of the largest surveys on LVH in CKD patients, the prevalence of LVH among patients with CKD and GFR > 60 mL/min/1.73m^2 was 32%. This increased stepwise at more advanced stages to reach a prevalence of 75% in stage 4–5. It has

also been hypothesized in some studies that the presence of abnormalities of LV mass and LV function may act as a factor worsening renal function in CKD[29]. However, this phenomenon may simply reflect shared risk factors for heart and kidney disease.

Alterations in left ventricular function can classically be divided into two broad categories: diastolic dysfunction and systolic dysfunction. Diastolic dysfunction is often the first abnormality to be detected in many cardiac conditions and represents a frequent impairment in patients with moderate to severe CKD. In some studies, there were alterations in as many as 65% of the patients, in indices of diastolic function as determined by conventional echocardiographic methods, and as many as 82% showed diastolic dysfunction by tissue velocity imaging[30]. However, in the CRIC study[28] it was surprising to note that concentric LVH was not associated with progressively severe diastolic dysfunction.

Systolic function of LV (EF parameter) remained within normal limits in all patients with a noticeable tendency to decrease with the decline in eGFR in a study by Beata Franczyk-Skóra et al[31]. A progressive decline of LV ejection fraction with the increase in severity of renal failure was observed in one study[32]. However, Hayashi et al. did not observe significant impairment of systolic function even in patients with severe CKD[33]. According to various studies the average occurrence of LV systolic dysfunction ranges from 15-28% in patients on haemodialysis[31].

RISK FACTORS FOR CVD IN CKD:

Cardiovascular disease (CVD) is the most common condition causing morbidity and mortality in CKD patients, which can occur even at the earliest stages of CKD without manifest vascular disease [34]. A graded increase in CVD risk occurs with worsening renal function. Updated guidelines have not only recognized CKD as an independent CV risk equivalent, but have also recommended that CKD be considered the highest risk group for subsequent development of CVD [35].

Patients with CVD and CKD share many 'traditional' risk factors in common for formation of atheromatous plaque, such as hypertension, dyslipidaemia, diabetes mellitus, obesity and smoking, but it is now being increasingly observed that these factors do not completely account for the disproportionate increase in cardiovascular mortality in CKD patients as compared to the normal population[19]. Thus, risk factors for adverse cardiovascular events in CKD can be classified as "*Traditional*" and "*non-traditional*" **(Figure 2)**. Changes unique to CKD are the progressive accumulation of uraemic toxins, electrolyte abnormalities, metabolic acidosis, sympathetic nervous system and renin angiotensin aldosterone system activation, and volume overload that result in structural and functional abnormalities of the heart, termed uraemic cardiomyopathy [31].

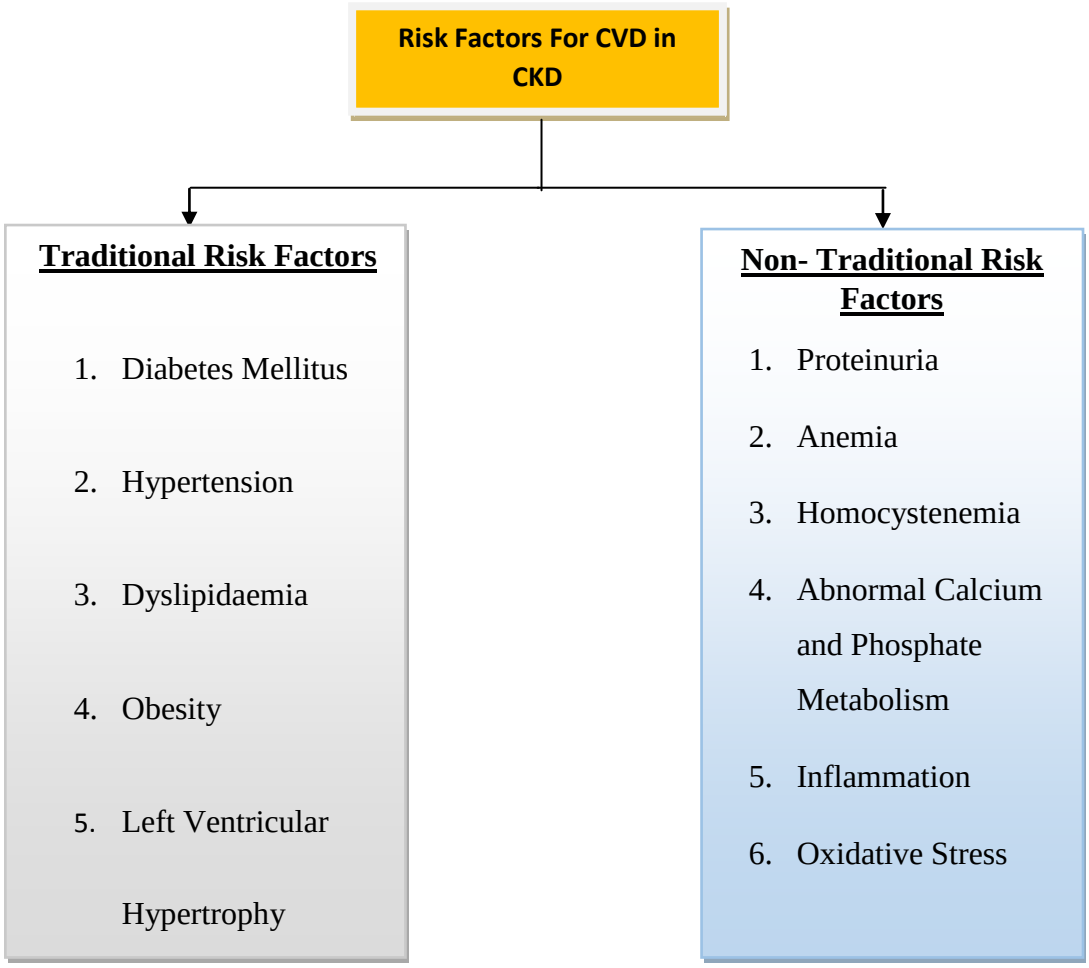


Figure 3: Interrelationship between traditional and non-traditional risk factors and cardiovascular disease and chronic kidney disease.

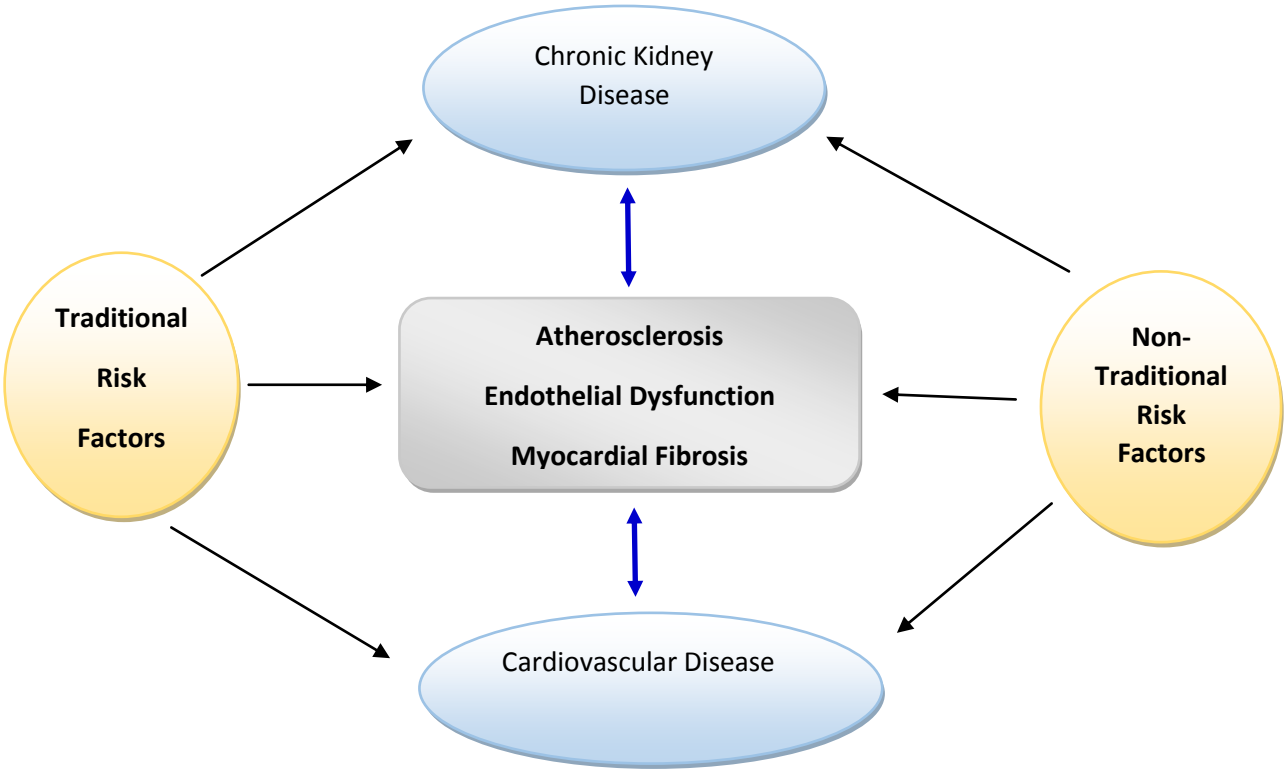


Figure 4: Pathogenesis of Cardiovascular Disease in CKD

TRADITIONAL RISK FACTORS:

Diabetes Mellitus:

A higher incidence of vascular disease occurs in patients with CKD associated with DM than with any other CVD risk factor. Hypertension (HTN) is also closely associated with DM: approximately 80% of patients with DM have co-existent hypertension [36].

The pathogenesis of vascular disease in diabetes is mediated through formation of advanced glycation end products (AGEs), which result from nonenzymatic post-translational modification by glycation and carbamylation in the AGE–RAGE (receptor for AGE) pathway [37].

This modification is mediated by the binding of sugar molecules with extracellular matrix or low-density lipoprotein (LDL), followed by oxidation. The AGEs deposit in the arterial wall, causing inflammation that heralds the formation of atheromatous plaque and a stream of subsequent events leading to endothelial injury and vascular disease. This endothelial injury manifests as albuminuria [37].

The occurrence of proteinuria has been linked to adverse cardiovascular outcome in patients with CKD. There is an exponential rise in mortality with the onset of proteinuria [38]. Standard management include good control of DM and proteinuria which can delay the onset of diabetic nephropathy. Blockade of Renin–angiotensin–aldosterone system (RAAS) pathway using a variety of drugs has reduced the incidence and progression of proteinuria[39,40]. The beneficial effect of RAAS blockade is not seen after nephropathy sets in, thereby emphasising the importance of early intervention.

Dyslipidemia:

Dyslipidemia which is defined as higher LDL and lower high-density lipoprotein (HDL) cholesterol, is another very important player in the sequence of events leading to atherosclerotic cardiovascular conditions in CKD patients.

Levels of HDL, an anti-atherogenic lipoprotein, has been found to progressively decrease as renal function declines, and the HDL that is produced is dysfunctional. In renal failure, apoA-I, synthesized by the liver, decreases as a result of which HDL cholesterol levels come down[41,42]. Levels of LDL cholesterol and triglycerides are found to increase with declining kidney function[19]. The impact of these alterations on

coronary artery disease is significantly higher than in the normal population without renal impairment[42].

In patients with CKD high levels of urea dissociates to form cyanate, which in turn leads to carbamylating of proteins. Carbamylated LDL causes progression of atherosclerosis by causing endothelial cell injury, increased expression of cell adhesion molecules, and proliferation of vascular endothelial smooth muscle cells. It also activated endonuclease G that leads to cellular injury and production of oxidants. High carbamylated LDL is an independent risk factor and predictor of CAD, future AMI, stroke, and death[43].

Lipoprotein A and apolipoprotein A also play important roles in atherogenesis. Statins have been shown to have beneficial effects on occurrence of CVD events in primary and secondary prevention, including in patients with CKD stages 1–4. However substantial benefits of statins when used in patients on haemodialysis is lacking.

Patients on haemodialysis (HD) predominantly have hypertriglyceridemia because of accumulation of very-low-density lipoprotein and intermediate-density lipoprotein, and lower levels of HDL[44]. Although patients with advanced CKD are at increased risk of CV events, there is a disinclination to use statins for several reasons. This is because unlike individuals in the general population, patients with CKD are at an increased risk of malnutrition and inflammation that have a cholesterol-lowering effect.

In a German diabetes and dialysis study, atorvastatin had no effect on the composite endpoint of CVD and non-fatal acute myocardial infarction in patients with DM undergoing HD [45].

In the AURORA study, rosuvastatin lowered LDL cholesterol in HD patients, but had no significant effect on the primary endpoint of death from CV causes, nonfatal AMI, or nonfatal stroke [46].

A meta-analysis provided strong evidence that in CKD, across a broad range of functional categories, including patients undergoing dialysis, statins reduce the risk of major vascular events, CV death, and all-cause death [47]. In 2013, guidelines from the American College of Cardiology and the American Heart Association recommended high-intensity use of statins for all patients with CVD and CKD[48].

Hypertension:

The occurrence and prevalence of hypertension goes up with declining renal function in patients with CKD. Various studies state that more than 90% of patients with end stage renal disease have been found to have Hypertension. The various mechanisms that have been put forward for the increased prevalence of hypertension in CKD are, secondary to volume expansion, sodium retention, and activation of RAAS and the sympathetic nervous system. Hypertension has also been shown to elevate renovascular resistance and the filtration fraction of sodium, particularly in the elderly[49]. An entity termed "non-dipping" occurs in patients with declining renal function, where there is absence of normal nocturnal physiologic dip in Blood Pressure. The loss of nocturnal dipping has been observed to elevate the incidence of adverse cardiovascular events in this set of population[50].

With progression of CKD, the hypertension that occurs as a result of CKD, tends to increase, thus establishing a vicious cycle[51] because poorly controlled hypertension

itself can in turn lead to progression of renal disease. Widened pulse pressure (a measure of arteriosclerosis) in HD patients has also been linked with an increased risk of death[52]. Optimal control of hypertension has been proven to reduce CVD risk in patients with CKD.

Management of hypertension in CKD is predominantly achieved by RAAS blockade, because stimulation of RAAS is the primary mechanism involved in hypertension occurring in these patients. As opposed to a step-up approach aggressive management of hypertension was shown to halt the progression of CKD and mortality [53]. The Irbesartan Diabetic Nephropathy Trial revealed a reduction in CV mortality and HF with lower achieved systolic BP (to 120 mmHg) [54]. In patients with hypertension even very small reductions in BP can have major beneficial effects with respect to CV outcomes [55].

Left ventricular hypertrophy:

The most common cardiac abnormality detected in patients with CKD is Left Ventricular Hypertrophy (LVH). As discussed earlier, strong risk factors for LVH are hypertension, anaemia, advancing age, diabetes mellitus, tobacco use, serum calcium, elevated, serum parathyroid hormone and hypoalbuminemia and these have been positively correlated with the occurrence of LVH.

Coronary artery calcification score, widened pulse pressure, and oxidative stress markers have also mentioned as important as risk factors[56]. Numerous studies have mentioned that the occurrence and prevalence of LVH rises with declining glomerular

filtration rate (GFR) and renal function, and also on commencement of dialysis, LVH is present in 75% of patients[57].

In the Dialysis Mortality and Morbidity Study Wave 2, Left Ventricular Hypertrophy was noted to be present in 17% of patients who were newly diagnosed with end stage renal disease. In patients Co-Existence of Left Ventricular Hypertrophy in patients with CKD is associated with poor Cardio-vascular outcomes. Left ventricular mass, that is indexed to height or body surface area (to prevent malnutrition and fluid overload from distorting measurements pertaining to LVH) is a very important and independent predictor of survival and CV events in CKD and patients on dialysis [58].

Cigarette Smoking:

Smoking has been shown to exponentially increase the risk for kidney disease. As widely known, it is also one of the main modifiable risk factors for CVD in the normal population as well as CKD patients. Nicotine has been shown to totally adversely alter systemic and intrarenal hemodynamics by stimulating postganglionic sympathetic nerve endings while smoking[59]

The resultant surge in plasma epinephrine and norepinephrine results in abnormal increase in BP. Beta-receptor– mediated renin and angiotensin II production increases renal vascular resistance[60]. Smoking also causes impaired response by the kidneys to elevated BP and increases GFR and intraglomerular pressure[61]. Smoking also has non-hemodynamic effects such as endothelial dysfunction, activation of growth factors, and insulin resistance, and an association of cigarettes smoked of high-normal albuminuria and microalbuminuria [62].

Cessation of Smoking has to be a very important corner stone in management of patients with CKD because it can substantially reduce CVD mortality rates in patients with CKD [63].

Obesity:

Numerous reports have shown strong association between visceral obesity and occurrence of CV events in patients with CKD[64]. But, as compared to the normal population, it has been observed that patients on dialysis have been found to have lower CV risk with higher BMI[65]. This has been termed "reverse epidemiology" or "obesity-paradox" which reflects the understanding that increased body mass index in patients on dialysis is a pointer towards adequate nutrition status. Some components of metabolic syndrome confer a high risk for CV events in the general population that cannot be totally extrapolated to patients with CKD as data in CKD patients are lacking.

Non- traditional risk factors

A number of studies have shown that traditional risk factors for CVD like the ones mentioned above, that are likely to be present in the general population do not necessarily account for the increased prevalence of CVD in patients with CKD. Many studies and observations in patients with CKD over the years have implicated multiple non traditional risk factors that are likely to play a causal role that could lead to the occurrence of CVD in this population.

Proteinuria:

Albuminuria plays a significant role in the pathogenesis of CVD. Significant trials like Heart Outcomes Prevention Evaluation (HOPE), Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) and Prevention of Renal and Vascular End-stage Disease (PREVEND) have shown significant associations between albuminuria and CVD events[66]. Microalbuminuria has been closely linked with the occurrence of CVD and other cardiovascular alterations like LVH, carotid intima media thickness, and myocardial ischemia [67,68,69].

In patients with hypertension and Left Ventricular Hypertrophy co- occurrence, the LIFE study showed that microalbuminuria is an independent risk factor for increased CV mortality and morbidity [70].

The HOPE trial showed that, in patients with diabetes mellitus, the presence of microalbuminuria was linked to an increased risk of occurrence of cardiovascular events which included acute myocardial infarction, stroke and CVD related and all-cause mortality.

A number of mechanisms have been proposed for the occurrence of adverse CV outcomes in diabetic patients with microalbuminuria viz.,

• Patients with microalbuminuria might also have increased prevalence of other co-existant risk factors.

• Endothelial dysfunction, vascular permeability, and abnormalities in coagulation and fibrinolysis occur in patients with diabetes [73]

• Markers of Chronic inflammation might also be associated with microalbuminuria [73]

• Microalbuminuria is also an useful indicator of end-organ damage.

The same factors as mentioned above might also be responsible for the occurrence of CVD events in non-diabetic patients with microalbuminuria. Microalbuminuria can progress to frank albuminuria in patients with or without DM, and these patients ultimately progress to decrease in renal function [73].

As mentioned previously it is important to note that microalbuminuria can identify patients at risk of progressing to renal insufficiency even before rise in creatinine occurs.

Anaemia:

Presence of Anaemia leads to hyperdynamic circulation and diffuse vasodilatation, both of which will ultimately lead to stimulation of neurohormonal system and subsequently salt and water retention.

Anaemia can result in left ventricular (LV) systolic dysfunction and left ventricular hypertrophy (LVH) subsequently heightening the risk of cardiovascular morbidity and mortality in CKD. That LVH is a reliable and acceptable predictor of morbidity and mortality has been shown in numerous studies [74].

2423 patients with CKD were included in a study by Weiner et al[75] and it was concluded that the presence of both anaemia and LVH conferred a very high risk for the occurrence of cardiovascular events like Myocardial Infarction, abnormal cardiac geometry and cardiac failure. Reduced production of erythropoietin, dietary deficiency of Iron, increased hepcidin levels due to anaemia of chronic disease are some of the reasons implicated in the development of anemia in patients with CKD[75].

One of the primary aspects in the management of anaemia in this population is erythropoietin replacement in addition to replenishment of Iron and Vitamin B12

stores. It has to be considered that increasing haematocrit and haemoglobin levels to a normal value has been linked with increased CV mortality in patients on hemodialysis with congestive cardiac failure and ischemic heart disease[76].

Anaemia has been long implicated in the pathogenesis of left ventricular hypertrophy in patients with Chronic Kidney Disease. In one blinded study, correction of anaemia with recombinant human erythropoietin showed regression of LVH [77]. Anaemia in CKD can also be inflammatory anaemia that is usually normocytic.

Abnormal calcium phosphate metabolism:

Serum phosphorus has emerged as a significant cardiovascular risk factor in patients with CKD[78]. It has also been reported that serum phosphorus even in the normal levels can result in cardiovascular events in patients with coronary artery disease [79] and Type 2 Diabetes [80]

Many studies have shown that the predictive value of a single serum phosphate measurement for cardiovascular risk is greatest for fasting morning concentrations. Hyperphosphatemia and hyperparathyroidism were found to be closely linked to all-cause mortality and Cardiovascular events in patients undergoing hemodialysis [81].

Possible pathophysiologic mechanisms that link serum phosphorous to increased risk of CVD events include vascular calcification and stiffening which in turn results in pulse pressure increase, reduction in coronary perfusion pressure, and finally LVH [82].

In addition to phosphorous and calcium, another very significant factor that has been implicated in the association of increased CVD events with phosphorous levels is the phosphaturic hormone FGF23 (Fibroblast Growth Factor 23) that is secreted by osteoclasts [83]. Numerous cross-sectional studies across various stages of renal dysfunction have reported that FGF23, in addition to being a highly sensitive

biomarker of phosphate toxicity, has also been found to exhibit a direct end organ toxic effect on the heart [83].

FGF-23 has been reported to be directly associated with incidence of LVH, vascular higher LV mass index and LVH, which in turn puts the patients at risk of having congestive heart failure and arrhythmias[84]. Many reports have also linked elevated FGF23 to progression of ESRD and mortality [83].

The Homocysteine in Kidney and End Stage Renal Disease (HOST) study showed that high FGF 23 levels exceeded all traditional cardiovascular risk factors and increased the risk of acute coronary syndrome and also all-cause mortality[84]. It was shown that higher FGF23 resulted in defective vasoreactivity, endothelial dysfunction and increased arterial stiffness [84]. Inhibition of FGF23- Klotho axis as a potential therapeutic strategy needs to be evaluated.

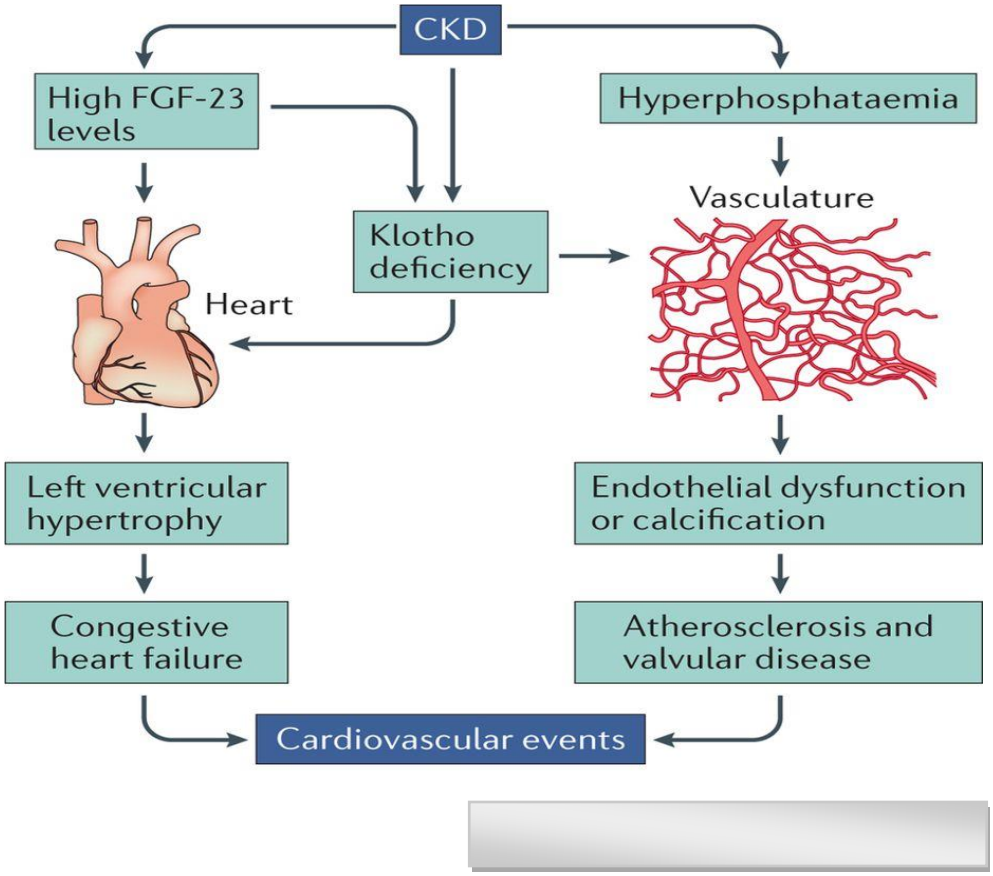


Figure 5: Patients with CKD often have hyperphosphataemia and high circulating levels of FGF-23. High levels of FGF-23 might directly induce left ventricular hypertrophy by stimulating pathological hypertrophic gene transcription in cardiomyocytes. In parallel, hyperphosphataemia and klotho deficiency disturb endothelial cell function and augment arterial wall calcification and valvular disease. These two processes might contribute to the high burden of cardiovascular events in CKD [86]

Inflammation:

Chronic Kidney Disease is now being increasingly identified as a chronic inflammatory entity, with defective adaptive and innate immunity [87]. An accumulation of uremic toxins occurs in patients with CKD which in turn results in a state of widespread inflammation. Perpetual inflammation leads to malnutrition–inflammation–atherosclerosis and calcification syndrome that has been linked to adverse CV outcomes [88]. High levels of fibrinogen, C- reactive protein (CRP), factor VIIc, factor VIIIc, interleukin 6, plasmin–antiplasmin complex, tumour necrosis factor α, D-Dimer and low levels of albumin have been detected in CKD patients and have been implicated in the mediation of CVD [88].

Dialysis, which is the cornerstone in the management of patients with ESRD has been found to only partially remove these toxins. In fact hemodialysis itself has been implicated in exposing the patients to the risks associated with membrane bio-incompatibility, long-term indwelling catheters, endotoxin leaks through back-filtration, and infections[89].

Peritoneal dialysis has also been implicated in promoting inflammation by causing an alteration in the metabolic milieu by increasing glucose level, reducing pH, and by the presence of glucose degradation products in dialysate[87].

Regardless of the multitude of mechanisms that initiate and promote inflammation, it has been proven beyond doubt that chronic inflammation causes vascular injury, initiating accelerated atherosclerosis[90].

CRP which has been found to increase with declining renal function mediates several key processes in the pathogenesis of atherosclerosis from initiation of plaque formation, promotion and finally rupture leading to adverse events [91]. It has been shown that more than one third of patients with ESRD have increased CRP levels that put them in the high-risk category for prediction of occurrence of adverse cardiac events [92].

Recently, neutrophil-to-lymphocyte ratio has been added as a marker for CVD events in patients with CKD. An increased neutrophil-to-lymphocyte ratio has been found to be independently associated with impaired endothelial function and can also potentially predict the occurrence of CV events [93]. High levels of neutrophil gelatinase–associated lipocalin can predict future CV events in this population [94].

Another novel marker, Asymmetric Di-Methyl-Arginine (ADMA) has been shown to inhibit endogenous nitric oxide synthase (NOS) leading to endothelial dysfunction. ADMA levels have been shown to increase with declining renal function, and studies have also shown a positive correlation with high ADMA levels and cardiovascular events and mortality **[96]**

Muscle wasting and cachexia:

Muscle, fat wasting and cachexia are highly prevelant in both CKD and Heart failure and is one of the most important risk factors for morbidity and mortality in this population [97]. Both cardiac cachexia and renal cachexia are multifactorial[97].

Reduced nutritional intake secondary to anorexia and decreased absorption of nutrients are factors that result in muscular atrophy and contribute to cachexia in patients with CKD and Cardiac failure[98]. Neurohormonal RAAS pathways and other inflammatory mediated pathways have also been shown to play major roles in the sequence of events leading to cachexia. The RAAS, which has been implicated in the pathogenesis of heart failure and CKD, is an important contributor to cachexia[99]

Association of CVD with CKD:

There is increased prevalence of CVD events in patients with CKD due to following reasons:

1. Almost all patients with CKD have concomitant risk factors for CVD [1]
2. On its own, CKD is an independent risk-factor for CVD [100]
3. The existence of CVD portends a faster reduction in renal function, thus establishing a vicious cycle [100]
4. Myocardial and arterial remodelling form the central pathway in the pathogenesis of CVD in patients with CKD. Myocardial remodelling occurs as a consequence of pressure and volume overload[101].

Chronic Kidney Disease predisposes the patient to both pressure and volume overload. Pressure overload occurs secondary to increased prevalence of hypertension, Diabetes

Mellitus, aortic stenosis, arteriosclerosis and anemia, eventually leading to Left Ventricular Hypertrophy. Volume overload can occur as a result of salt and water retention, anaemia, congestive cardiac failure, arteriovenous shunting in dialysis and hypoalbuminemia resulting in left ventricular dilation.

The uremic environment and IHD also produce an increase in myocardial cell apoptosis that accelerates the cardiomyopathy, resulting in both systolic and diastolic dysfunction [102].

Mark et al. [103] revealed in their study that LVH is the main myocardial geometrical alteration specific to uraemia and other alterations like dilation of LV and systolic dysfunction are usually secondary to co - existing Ischemic Heart disease.

Alterations in Left Ventricular Geometry in CKD

The prevalence of Left ventricular (LV) mass and geometrical changes and LV dysfunction progressively increase from stage 2 to stage 5 in CKD [104]. LVH prevalence increases step wise from stage 2 through stage 5 as renal function declines and 70–80% of patients with chronic kidney disease present with established LVH which is of the concentric type in the majority [28, 105].

Structurally, myocardial hypertrophy can be categorised into concentric and eccentric[107]. The muscular component of the LV (LV wall) prevails over that of the cavity component (LV volume) in concentric hypertrophy. Due to the increased thickness and myocardial fibrosis in patients with concentric LVH, there is a reduction in compliance of the left ventricle and eventually the end-diastolic volume becomes soo small that it becomes insufficient to maintain cardiac output under dynamic physiological demands (diastolic dysfunction) [108].

In eccentric hypertrophy, tensile stress elongates myocardiocytes and increases LV end-diastolic volume [109]. The LV walls are relatively thinner and with reduced ability to contract (systolic dysfunction). Severe anaemia and volume excess are the major factors that result in eccentric LVH [110].

Though nuclear magnetic resonance is the most accurate technique available for estimating LV mass and function in patients with heart disease, quantitative echocardiography is even now the most commonly used mode of detecting alterations in LV mass and function in CKD[111].

Persistently increased LV mass along with the occurrence of myocardial fibrosis, predisposes the patients with CKD to numerous risks. Myocardial fibrosis results in decreased diastolic compliance thereby impairing diastolic filling. Ventricular dilatation (dilated cardiomyopathy) can also result as a part of background ischemic heart disease which can result in systolic dysfunction. Thus, both systolic and diastolic congestive heart failure can take place.

Hemodialysis itself has also been shown to produce a phenomenon called "myocardial stunning" wherein regional wall motion abnormalities develop secondary to transient ischemic events[112]. Thus, recurrent episodes of "myocardial stunning" can lead to significant alterations in cardiac structure, geometry and function.

The development of LVH and its persistence and severity are very closely associated with heightened mortality risk[113]. It has also been shown in a study by London et al[117] that a 1.0 g reduction in LV mass resulted in a 1% decrease in mortality over 5 years in a patient cohort who were treated with conventional hemodialysis. Thus it has been shown that LVH regression is associated with a decreased risk of mortality.

Different mechanisms that operate concurrently or sequentially in individual patients have been proposed; Hence dissection of pathophysiological pathways leading to the occurrence of LVH in patients with CKD is quite complex.

Proposed factors leading to alterations in LV geometry have been broadly divided into three broad categories [118]:

1) Factors pertaining to Afterload (systemic arterial resistance and larger vessel compliance);

2) Factors pertaining to Pre-load (Anemia, increased extracellular fluid volume, large flow arteriovenous fistulas); and

3) Non-after-load or Non Pre-load related factors such as metabolic alterations, cytokines, neurohumoral factors, oxidative stress and inflammmation, and activation of intracellular mediators by “uremia”.

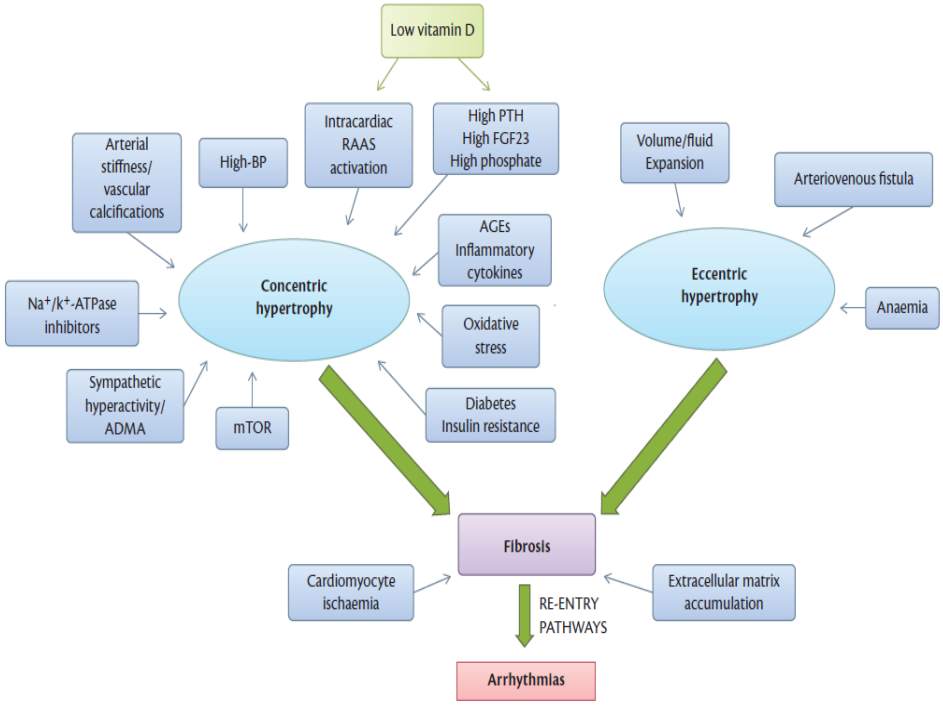


Figure 6: Various pathophysiological mechanisms involved in causation of LVH in CKD

PULMONARY ARTERY HYPERTENSION IN CKD :

Pulmonary hypertension (PH), which is defined by AHA as systolic pulmonary artery pressure (SPAP) > 25 mmHg at rest as determined by Doppler echocardiography, is a common co-morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease with a high but variable prevalence[119,120]. The prevalence of PHT in ESRD patients was reported to be around 40–50% in a recent study [121]. More importantly, the existence of PH has been linked with high risk of morbidity and mortality in CKD patients [122]

In addition, the pathogenesis of PH in CKD has not been well elucidated. Many different mechanisms have been proposed to play a role: pulmonary artery calcification as a result of hyperparathyroidism; hemodynamic changes due to presence of arteriovenous fistula (AVF), endothelial dysfunction due to increased

oxidative stress from uremic toxins, chronic inflammation [123]. In addition to all these factors, patients with CKD also have concomitant left ventricular disease, chronic lung disease, thromboembolic conditions, autoimmune conditions like scleroderma and systemic lupus erythematosus, and liver disease, that are also well-proven risk factors for developing PH. As a result of this, the World Health Organization (WHO) has categorized PH due to CKD and end-stage renal disease under WHO Group 5, "miscellaneous causes".

CARDIO-RENAL SYNDROME:

The so-called "cardiorenal syndrome" is a complex interplay involving multiple organ systems predominantly involving the heart and the kidneys. Any overt or covert affliction of the heart or kidney can adversely involve the other organ and vice versa. As per the definition proposed by the Consensus conference on Acute Dialysis Quality Initiative Group the term cardio-renal syndrome (CRS) has been defined as 'disorders of the heart and kidney whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other' [124].

The National Heart, Lung and Blood Institute defines it as "A state in which therapy to relieve heart failure symptoms is limited by further worsening of renal function".
More often than not, by the time of clinical presentation, multiple components of the interconnected network of events get involved. It is not practically possible to definitely say if kidney or the heart was the first to trigger the sequence events most of the time. Other than haemodynamic interactions, there are many other factors that are implicated in the pathophysiology of cardiorenal syndrome, all of which can be potential targets for management.

As per the Consensus Conference by the Acute Dialysis Quality Group CRS has been essentially divided into two main groups, cardio-renal and reno-cardiac CRS, on the basis of the which organ was the initiator of the disease (cardiac or renal) [125].

Then, both cardio-renal and reno-cardiac CRS are classified again into acute and chronic, according to disease's temporal onset. The last type, Type 5 of CRS integrates simultaneous cardio- renal involvement that is triggered by a systemic disease like sepsis, etc. [125]

Table 2: Classification of Cardio-Renal Syndrome (CRS) [125]

Type	Denomination	Description	Example
1	**Acute cardiorenal**	Heart failure leading to AKI	Acute coronary syndrome leading to acute heart and kidney failure
2	**Chronic cardiorenal**	Chronic heart failure leading to CKD	Chronic heart failure
3	**Acute reno-cardiac**	AKD leading to acute heart failure	AKI related uremic
4	**Chronic reno-cardiac**	CKD leading to heart failure	Left ventricular hypertrophy and diastolic heart failure due to CKD
5	**Secondary**	Systemic disease leading to heart and kidney failure	Sepsis, vasculitis, diabetes mellitus, amyloidosis

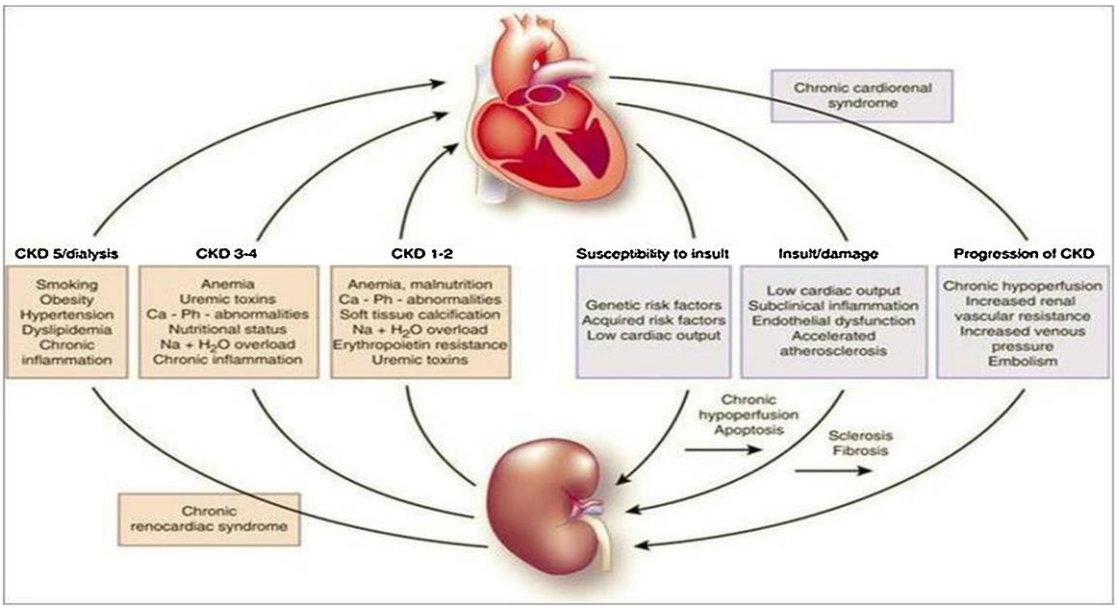


Figure 7: Cardiorenal Syndrome – A complex interplay between Kidneys and the Heart

<u>Cardio Renal Syndrome- 2</u>

CRS type 2 (CRS2) is described by chronic malfunctioning of the heart leading to progressive decline in renal function. The temporal link between the heart and kidney disease happens to be a major facet of the definition. Advancing CKD resulting from chronic heart failure in congenital or acquired heart disease or from recurrent bouts of acute decompensated heart failure are some examples of CRS-2.

As has been already alluded to, CKD has been variously reported from 26–63% of patients with CHF [126,127]. Though numerous research studies have taken place in this regard, most studies have failed to conclusively demonstrate which of the two disease processes was primary initiating event, thus presenting challenges when trying to classify patients into the CRS subtype definitions.

It has been proposed that chronic renal hypoperfusion may progressively lead to adverse alterations in renal vasculature; high renal vascular resistance and persistant activation of hormonal systems all contribute to further impairment of renal function thus progressing from an initial insult to a increasing fibrosis and sclerosis of the renal parenchyma [129].

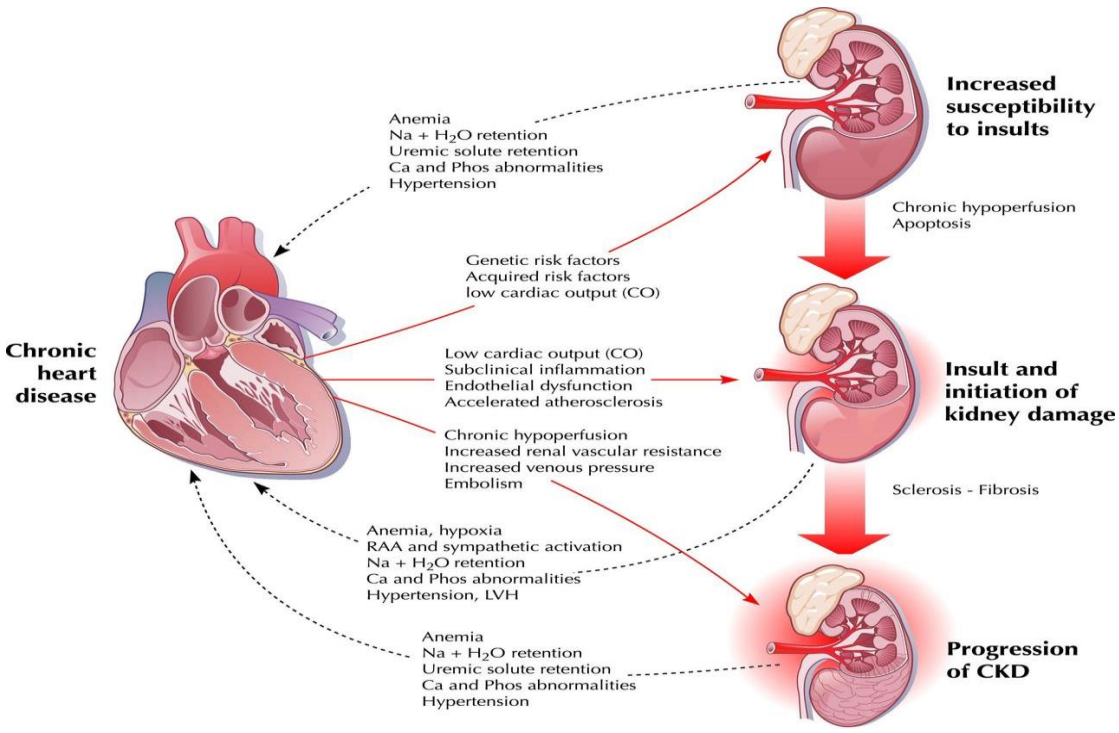


Figure 8: Predominant pathophysiologic mechanisms of CRS2 in stable chronic HF [128]

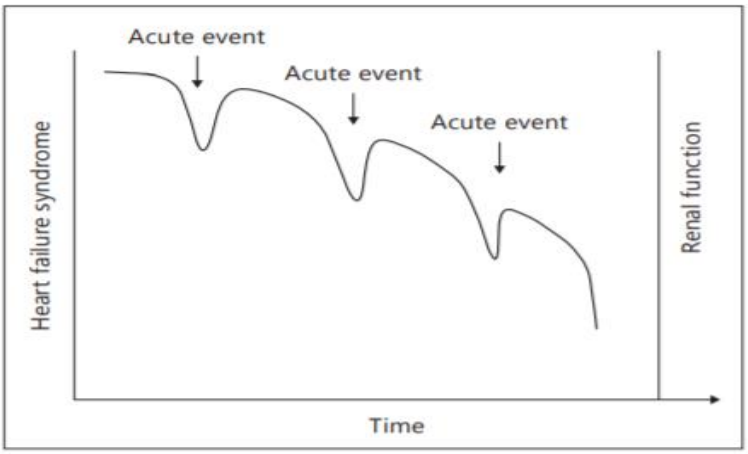


Figure 9: Recurrent Acute Events (Decompensated Heart Failure and/or acute kidney injury) might play a role in worsening of chronic heart and kidney dysfunction [128]

Activation of neurohumoral system, hypoperfusion of the kidneys and high venous pressure, atherosclerosis, inflammation and oxidative stress together account for primary pathophysiological mechanisms underlying type 2 CRS [129]. These factors get triggered during recurrent bouts of acute heart and/or renal decompensation as shown in figure 7, which eventually results in HF and CKD progression**.**

CARDIO-RENAL SYNDROME 4

Type-4 CRS termed as chronic reno-cardiac disease, is described as cardiovascular dysfunction in patients with chronic kidney disease at any stage according to National Kidney Foundation (NKF) classification[130]. As discussed previously, that renal dysfunction is an independent risk factor for occurrence of cardiovascular events with heightened risk of mortality for Acute Coronary events and sudden death in CKD[130].

Chronic kidney disease independently hastens ischemic heart disease and makes the heart susceptible to pressure and volume overload resulting in left ventricular hypertrophy[131]. Activation of the neurohumoral system (RAAS pathways), volume

excess, endothelial dysfunction, anaemia, inflammation and oxidative stress, all of which lead to functional and structural changes in the heart and vessels [132]. A baseline GFR of less than 60 ml/min−1/1.73m^2 is independently associated with heightened of CHF[133]. As shown in figure 8 numerous factors can promote cardiac dysfunction in patients with CKD.

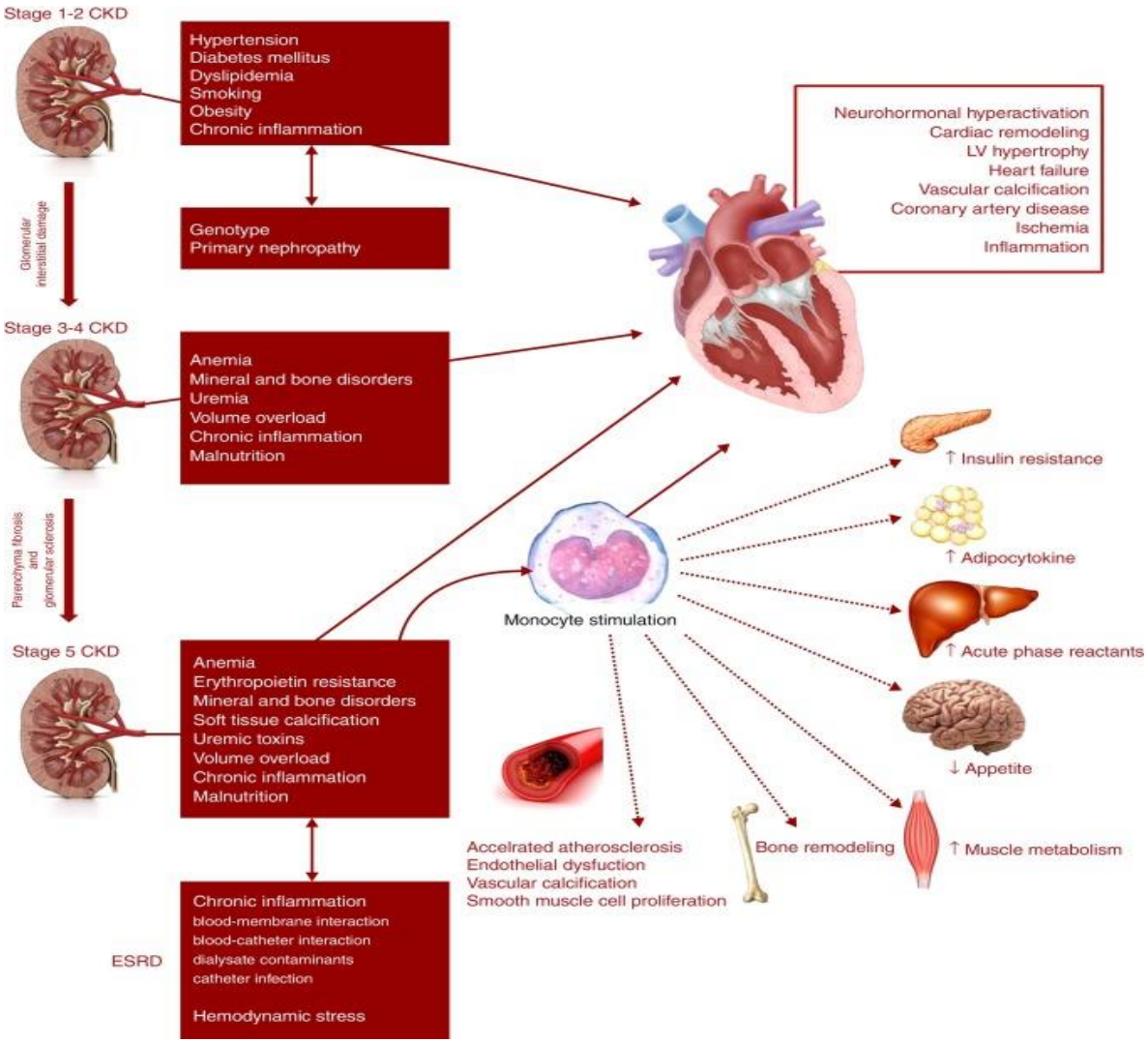


Figure 10: Pathophysiological mechanisms leading to CRS-4

DIAGNOSIS OF CVD IN CKD

The definitive triad consisting of symptoms of ischaemia, ECG changes and increased cardiac biomarkers is unlikely to be encountered in patients with CKD, making a diagnosis of CAD difficult and demanding. In addition, there also seems to be a dearth of information on the usefulness of various diagnostic methods in CKD patients because patients with renal dysfunction have been excluded from major randomised trials and also in part due to reduced negative predictive value of these tests as a result of increased CAD prevalence in this population [134]

As extensively discussed, structural and functional cardiac abnormalities are highly prevalent in CKD patients. ECG is the extensively available diagnostic modality in resource-limited settings. Abnormalities in ECGs are not uncommon and one study reported that 46% of the enrolled CKD patients had some abnormality[135]. Nevertheless, ECGs can be helpful in detecting LVH and bundle branch blocks.

Two-dimensional (2D) transthoracic echocardiography is also becoming increasingly available, and can be utilised to detect LVH, regional wall motion abnormalities, valvular calcification and Ejection fraction but it has to be noted that it is operator dependent. Reduced exercise tolerance in CKD patients has resulted in low utility of this modality. Cardiac MRI is particularly useful to detect myocardial scarring.

Coronary artery stenosis can be identified using stress cardiac magnetic resonance with a sensitivity of 100% and a specificity of 90% but its limitations are high cost, non-availability and it cannot be used in CKD patients with GFR <30 mL/min/1.73 m^2. CT angiography has been reported to have high sensitivity and specificity in

normal population but it's in CKD is limited as presence of significant coronary calcification precludes it's use in this population.

The usefulness of myocardial perfusion studies in detecting CKD patients to predict future risk of CAD was demonstrated in the meta-analysis by Rabbat et al[136]. Pertaining to the use of non-invasive tests based on comorbid illnesses, myocardial perfusion scintigraphy (MPS) has been found to be better in patients with resistant hypertension and arrhythmias.

Serum biomarkers that are commonly used in normal, non-CKD population are not very specific for myocardial necrosis as they have been found to be elevated even in the absence myocardial necrosis. This increase is because of silent micro infarction and myocardial apoptosis[136] and not secondary to decreased renal clearance as previously though.

Pertaining to cardiac troponins (cTn), though it was believed that cTn-I is more specific than cTn-T initially, no guideline recommends superiority of one troponin over the other. The general consensus has been that serial values as compared to a single value in non-CKD patients has to be considered for diagnosis of acute myocardial infarction in patients with CKD.

Table 3: Usefulness of various diagnostic modalities for diagnosis of cardiovascular disease in CKD [137]

Diagnostic Modality	**Comment**
ECG	Has to be done yearly; to look for LVH & rhythm
Resting Echocardiogram	LV function, RWMA , valvular disease ; operator dependent
Cardiac SPECT	Sensitivity is variable ; effect of antihypertensive agensts ; good negative predictive value
Dobutamine stress echocardiography	More specific than SPECT for CAD; LVH is confounder; exercise intolerance
Stress CMR	Good sensitivity and specificity; not in eGFR < 30ml/min/m^2
Coronary CT angiography	Not in established CAD/ESRD; higher burden of coronary calcium confounder
Coronary angiography	Gold Standard; invasive, loss of residual renal function

CORNERSTONES IN MANAGEMENT OF CVD IN CKD

Aspirin, statins, ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) and β blockers form the corner stone of management of patients with CVD-CKD co-occurrence. Adequate control of blood sugar and hypertension are most important in CKD patients. It has to be noted that there is scarce literature on the optimal

management strategy of this subgroup of patients with CVD-CKD because almost all the major trials have excluded patients with renal dysfunction. Benefits secured from standard medical therapy in non-CKD patients cannot be extrapolated to the CKD population.

Observational studies have reported that optimal drugs are not being used adequately in patients with CKD. In a study by Berger et al[138] on more than 1000 patients on dialysis, patients with CKD were found not to be treated with optimal medical therapy though they were found to provide mortality benefit.

Antiplatelets have been the fundamental agents of therapy for CVD with an even in patients with CKD in almost all studies in literature. A meta-analysis by the Antithrombotic Trialists' Collaboration showed that low dose aspirin is as good as standard dose . There were no increases in major bleeding events independent of the stage of CKD in The UK Heart and Renal Protection (HARP) study and the Dialysis Outcomes and Practise Patterns Study (DOPPS).

A recent Cochrane collaboration systematic review in CKD patients across all stages of CKD showed that antiplatelet agents decreased the risk of myocardial infarction, but not all-cause mortality, cardiovascular mortality or stroke with increased incidence of bleeding episodes[139].

ACEi or ARBs are one of the cornerstones in patients with cardiovascular disease with normal renal function. The efficacy of ACEi/ARBs in renal insufficiency was shown to be undecided as Fosinopril in Dialysis (FOSIDIAL) trial did not show any further benefit in dialysis patients. A study by Efrati et al [140] showed decrease in mortality by 52% among patients on dialysis. Takayashi et al[141] showed that, Candesartan, an ARB

was shown to bring down cardiovascular mortality in patients with ESRD. Among Beta-Blockers, carvedilol was found to reduce mortality and risk of cardiovascular events in CKD [137]. In the meta-analysis by Badve et al [142], β blockers were found to improve all-cause mortality in CKD patients with chronic systolic heart failure across various stages of non-dialysis CKD patients.

With respect to statins, The Kidney Disease: Improving Global Outcomes (KDIGO) 2013 guidelines recommended that "statin or statin/ezetimibe treatment in adults aged ≥50 years with eGFR <60 mL/min per 1.73 m2 but not treated with chronic dialysis and in those between 18 and 49 years statin therapy is recommended if there are other risk factors for CVD."

Initiating statins in patients on dialysis has not been recommended but continuation of statin therapy if patient is already receiving it has been suggested. Manske et al [143] performed the only randomised controlled trial (RCT) until today, comparing medical and reperfusion techniques way back in 1992 with 26 patients with CKD and insulin dependent diabetes and with a follow-up of 2 years. Though there was suboptimal medical therapy in the subjects with only calcium channel blockers and aspirin, there was substantial benefit with revascularisation therapy [143].

The Coronary Syndrome Israeli Survey (ACSIS) compared different reperfusion techniques in patients with serum creatinine >1.5 mg% found 30-day mortality was 8.3% in the thrombolysis group as compared to 40% and 29.7% in the primary PCI and no reperfusion groups respectively[144]. Hobbach et al [145] had conducted a study on 352 CKD patients with ST segment elevation myocardial infarction (STEMI) and reported that 30-day and 6-month mortality decreased from 22% to 4% ($p<0.03$) and

from 25% to 7% ($p<0.05$) among those who were subjected to PCI during hospitalisation.

Most of the recommendations are based on observational data or post hoc analyses and more studies are further required to optimally manage patients with CVD-CKD co-occurrence.

Materials

&

Methods

SOURCE OF DATA:

This study was conducted on 64 patients diagnosed with Chronic Kidney Disease with no clinical features of heart failure attending the General Medicine outpatient section and inpatients of R.L.Jalappa hospital and research centre Tamaka, Kolar.

METHOD OF COLLECTION OF DATA:

Inclusion criteria:

- Ages Between 18 to 60 years
- Patients with established CKD as defined by CKD-EPI formula (< 60 ml/min/1.73 m^2) of more than 3 months associated with elevated serum creatinine and with or without albuminuria and with or without structural changes determined by ultrasonography with no features of Congestive cardiac failure.

Exclusion criteria:

- Prior transplantation
- Acute Kidney Injury
- Systemic or hematogenous malignancy
- Rheumatic Heart Disease & Congenital heart Disease
- Pre-existing cardiovascular disease like myocarditis due to infective aetiology, primary heart muscle diseases like cardiomyopathies
- Severe comorbid illnesses, such as cirrhosis, HIV disease, and severe (New York Heart Association class III or IV) Heart Failure and COPD (MMRC grade III or IV)

Method of collection of data:

This study was conducted on patients attending the general medicine outpatient section and inpatient of R.L.Jalappa hospital and research centre Tamaka, Kolar .Consecutive patients, diagnosed to have CKD who satisfy the inclusion and exclusion criteria were enrolled in the study after obtaining informed consent . A detailed history with regard to cardiac symptoms such as dyspnea, orthopnea , chest pain and palpitations were recorded. Physical examination was carried out to detect signs of cardiac failure and hypertension.

16 cases each of Stage 1 &2, 3, 4 and 5 based on eGFR were included in the final analysis adding up to a total of 64 to form the study group .

Laboratory investigations to detect elevated urea , creatinine, anemia , calcium and phosphorous metabolic abnormalities , proteinuria and dyslipidemia were undertaken. USG of Kidneys was done to measure the Renal size.

Participants were subjected to Chest X-Ray, ECG and Echocardiogram to detect pericardial , myocardial and endocardial changes .

2D–Trans thoracic Echocardiography machine was used with 3.5 MHz transducer prob and Two dimensional echocardiography and M- mode echocardiography were subsequently done on the subjects . The M-mode was recorded perpendicular to the long axis of and through the center of the left ventricle at the papillary muscle level was taken as standard measurements for systolic and diastolic wall thickness and other chamber dimensions. The LVEF was taken as measure of left ventricular systolic function. Diastolic function was determined by measuring E/A ratio by special Doppler inflow velocity (E is peak early diastole velocity and A is peak atrial filling velocity of left ventricle across mitral valve). E/A ratio less than 0.75 and more than

1.8 was considered as diastolic dysfunction. LVH was diagnosed when interventricular septum thickness or left ventricular posterior wall thickness was ≥ 12 mm. Left ventricular mass Index were calculated based on the above parameters. Peak trans-mitral flow E and A wave velocity, E wave deceleration time, were measured from the apical 4-chamber view

Ejection fraction calculated as:

LV EF (%) = LVVd-LVVs × 100

Normal=59.2±6%(LVVd)

LVVd: Left ventricle volume in diastole
LVVs: Left ventricle volume in systole

Sampling procedure:

An observational cross sectional study was performed. After obtaining approval from the Ethical Committee Board, consecutive patients, diagnosed to have CKD who satisfy the inclusion and exclusion criteria were enrolled in the study after obtaining informed consent. A detailed history with regard to cardiac symptoms such as dyspnea, orthopnea, chest pain and palpitations was recorded. Physical examination was carried out to detect signs of cardiac failure and hypertension. CKD patients were categorised based on eGFR into 4 groups and 18 cases each of Stage 1 & 2 (eGFR≥60ml/min/1.73m^2), 3 (eGFR 30-59 ml/min/1.73m^2), 4 (eGFR 15-29 ml/min/1.73m^2) and 5 (eGFR < 15 ml/min/1.73m^2) according to CKD-EPI formula were included in the final analysis adding up to a total of 64 formed the study group.

STATISTICAL ANALYSIS:

Sample size is estimated by using the formula,

$$\text{Sample size} = \frac{Z_{1-\alpha/2}^{2}\, p\,(1-p)}{d^{2}}$$

Here $Z_{1-\alpha/2}$ = Is standard normal variate (at 5% Type 1 error ($p < 0.05$) it is 1.96 and at 1% Type 1 error ($p<0.01$) it is 2.58). As in majority of studies P values P value below 0.05 is considered significant and hence 1.96 is used in the formula.

p = Expected proportion based on previous studies or pilot studies.

P = 74.4 or 0.743

q = 25.6 or 0.256

d = 15% or 0.15

Using the above values at 99% Confidence level a sample size of 72 subjects with CKD were included in the study.

Considering 10% Non - response a sample size of $65 + 6.7 \approx 64$ subjects were included in the study.

STATISTICAL METHODS

Descriptive Analysis: Descriptive analysis was carried out by Mean and Standard Deviation for quantitative variables, frequency and proportion for categorical variables.

Quantitative outcome:

The association between categorical explanatory variables and quantitative outcome was assessed by comparing the mean values. The mean differences along with their 95% CI were presented by Independent sample t-test.

Categorical outcome:

The association between explanatory variables and categorical outcomes was assessed by cross tabulation and comparison of percentages. Chi square test was used to test statistical significance.

Linear regression:

The association between quantitative explanatory and outcome variables was assessed by calculating Pearson correlation coefficient and the data was represented in a scatter diagram.

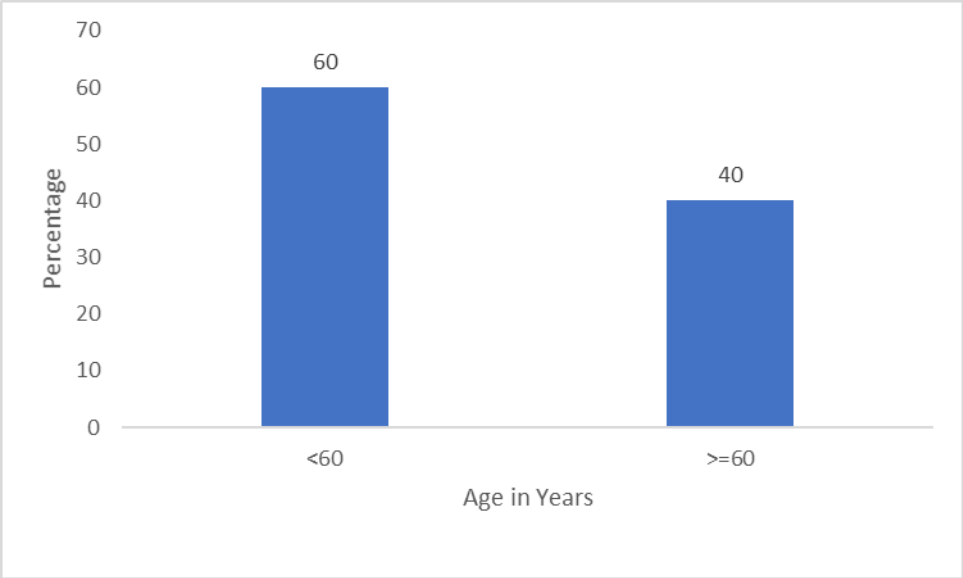
Univariate and Multi- variate linear regression analysis were also performed. P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis. [92]

RESULTS

Table 4: DESCRIPTIVE ANALYSIS OF AGE OF PATIENTS

Age of Patients	No. of Patients	Percentage
<60	39	60
>=60	25	40
TOTAL	**64**	**100**

Figure 11: AGE OF PATIENTS



The figure and table show that 60% of patients with CKD are below 60 years of age while 40% of the patients are above 60 years of age.

Table 5: DESCRIPTIVE ANALYSIS OF AGE OF PATIENTS

Parameter	Minimum	Maximum	Mean	Std. Deviation
Age [Years]	46	68	58.16	5.30

Table 6: ASSOCIATION BETWEEN AGE AND CKD STAGES

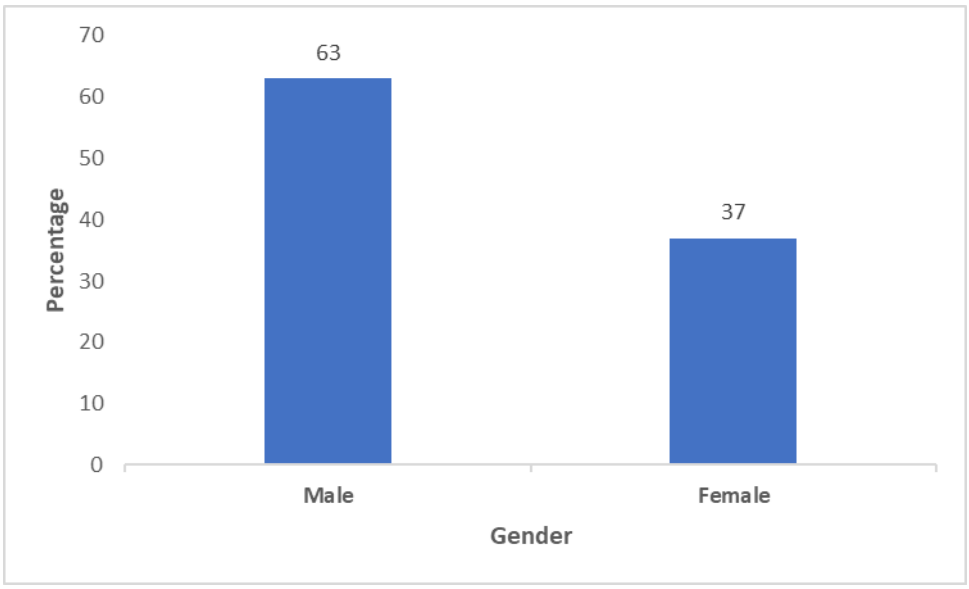
Parameter		Mean	Std. Deviation	P-Value (ANOVA)
AGE	Stage I & II	60.4	4.9	.003
	Stage III	54.4	3.0	
	Stage IV	60.1	4.5	
	Stage V	57.7	6.4	

The table shows that there is a significant difference in the age groups of patients in various stages of CKD. The mean age of CKD Stage I was 60.4 $\pm$ 4.9 years whereas it was 57.7 $\pm$ 6.4 years in CKD stage V.

Table 7: DESCRIPTIVE ANALYSIS OF GENDER OF PATIENTS

Gender of Patients	NO. OF PATIENTS	PERCENTAGE
Male	40	63
Female	24	37
TOTAL	**64**	**100**

Figure 12: GENDER OF PATIENTS



The figure above shows that 63% of patients were males and 37% were females.

Table 8: ASSOCIATION BETWEEN GENDER AND CKD STAGES

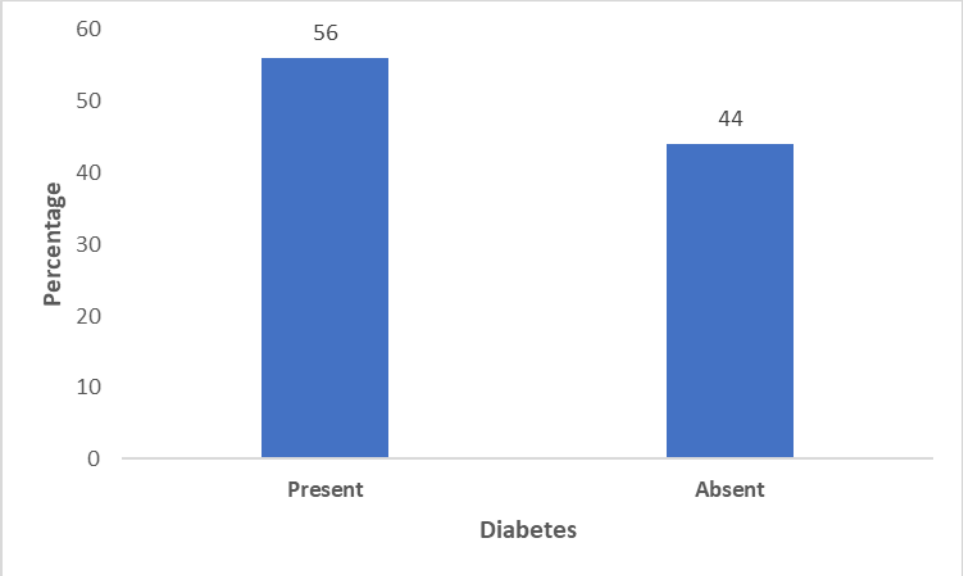
			CKD STAGES				P-Value χ^2
			Stage I & II	**Stage III**	**Stage IV**	**Stage V**	
GENDER	Male	Cases	9	12	9	10	.636
		%	56.2%	75.0%	56.2%	62.5%	
	Female	Cases	7	4	7	6	
		%	43.8%	25.0%	43.8%	37.5%	

The table shows that there is no statistically significant association between Gender and various stages of CKD.

Table 9: DESCRIPTIVE ANALYSIS OF DIABETIC STATUS

Diabetes	No. of Patients	Percentage
Present	36	56
Absent	28	44
TOTAL	**64**	**100**

Figure 13: DIABETIC STATUS



As shown in the Figure and table above, 56% of our cohort were Diabetics and 44% were Non-Diabetics.

Table 10: ASSOCIATION BETWEEN DIABETES AND CKD STAGES

			CKD STAGES				P-Value χ^2
			Stage I & II	**Stage III**	**Stage IV**	**Stage V**	
DIABETES	Yes	Cases	12	7	6	11	.061
		%	75.0%	43.8%	37.5%	68.75%	
	No	Cases	4	9	10	5	
		%	25.0%	56.2%	62.5%	31.25%	

The Table above shows that there is no significant association between prevalence of Diabetes and CKD stages.

Table 11: PRESENCE AND ABSENCE OF HYPERTENSION

Hypertension	**No. of Patients**	**Percentage**
Present	49	76
Absent	15	24
TOTAL	**64**	**100**

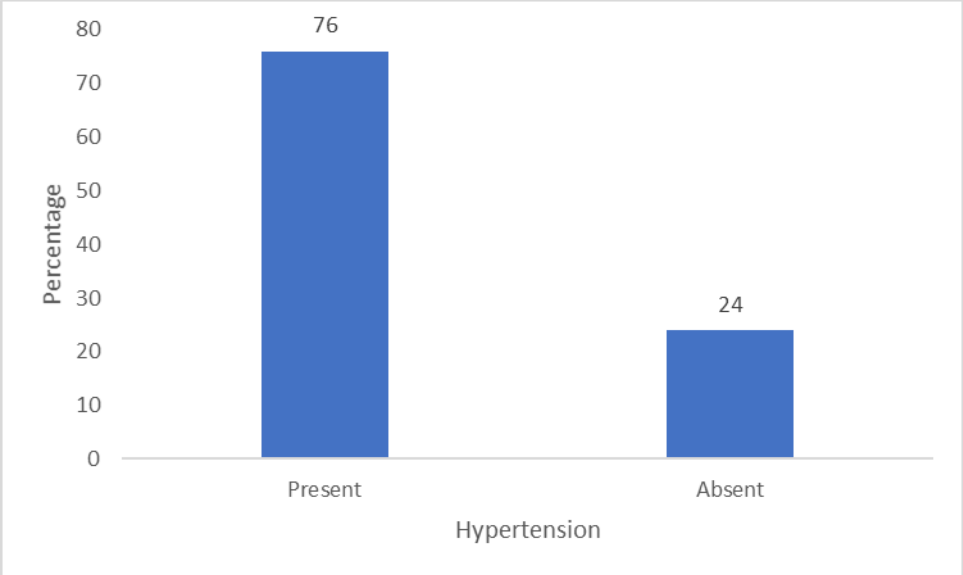
As shown in the Table 11 , 76 % of the cohort were hypertensives.

Table 12: DESCRIPTIVE STATISTICS OF BLOOD PRESSURE IN CKD

Parameter	Minimum	Maximum	Mean	Std. Deviation
Systolic BP [mm Hg]	110	180	154.35	14.57
Diastolic BP [mm Hg]	70	100	85.33	8.05

As shown in the Table 12 the mean systolic Blood Pressure of the cohort was 154.3 ± 14 mm Hg and the mean Diastolic Blood Pressure was 85 ± 8 mm Hg.

Figure 14: HYPERTENSION



As shown in figure above,76% of our cohort were hypertensives with Blood Pressure above 140/90 mm Hg.

Table 13: ASSOCIATION BETWEEN HYPERTENSION(HT)AND CKD STAGES

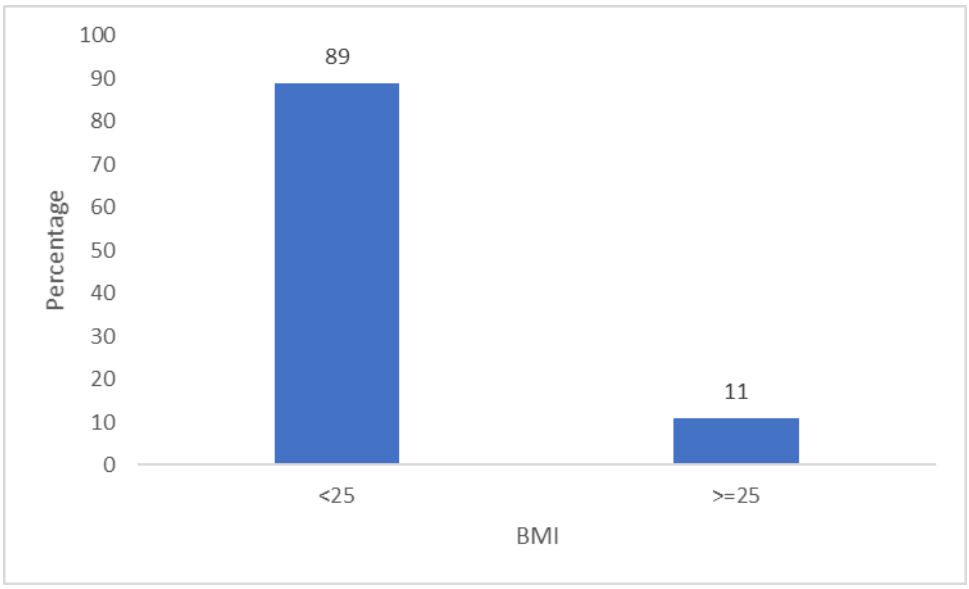
			CKD STAGES				P-Value χ^2
			Stage I & II	Stage III	Stage IV	Stage V	
HT	Yes	Cases	9	9	16	15	.001
		%	56.2%	56.2%	100.0%	93.75%	
	No	Cases	7	7	0	1	
		%	43.8%	43.8%	0.0%	6.25%	

The Table shows a statistically significant Association between hypertension and various stages of CKD. The prevalence of hypertension progressively increases from 56.2% in CKD Stage I to 93.7% in Stage V.

Table 14: BODY MASS INDEX

BMI	No. of Patients	Percentage
<25	57	89
>=25	7	11
TOTAL	**64**	**100**

Figure 15: BODY MASS INDEX



As shown in the table and figure above , 89% patients had a BMI level below 25 whereas 11% of them were in the overweight category of above 25.

Table 15: ASSOCIATION BETWEEN BMI AND CKD STAGES

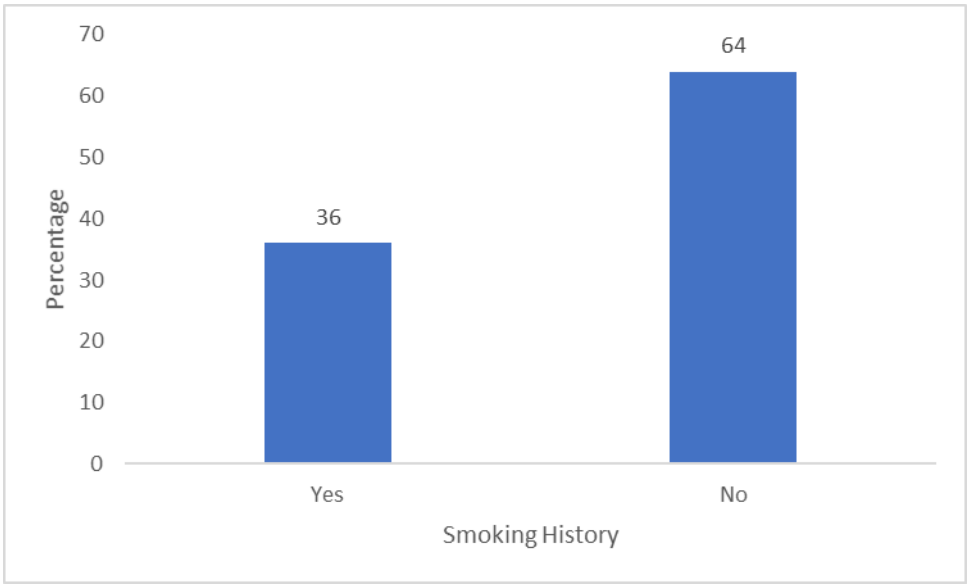
			CKD STAGES				P-Value χ^2
			Stage I & II	Stage III	Stage IV	Stage V	
BMI	<25	Cases	16	16	14	11	.009
		%	100.0%	100.0%	87.5%	68.75%	
	>=25	Cases	0	0	2	5	
		%	0.0%	0.0%	12.5%	31.25%	

The table shows that there was a statistically significant association between various stages of CKD and Body mass Index.

Table 16: SMOKING HISTORY

Smoking History	No. of Patients	Percentage
Yes	23	36
No	41	64
TOTAL	**64**	**100**

Figure 16: SMOKING HISOTRY



As shown in the table and figure, 36% of patients were current smokers whereas 64% of them were non- smokers.

Table No.17: ASSOCIATION BETWEEN SMOKING AND CKD STAGES

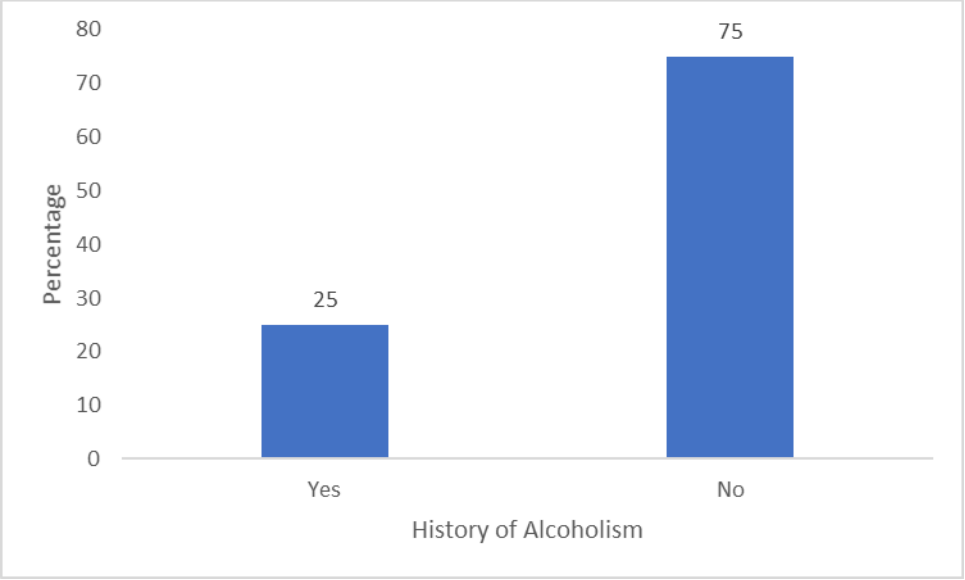
			CKD STAGES				P-Value χ^2
			Stage I & II	**Stage III**	**Stage IV**	**Stage V**	
SMOKING	Yes	Cases	3	6	7	7	.360
		%	18.8%	37.5%	43.8%	43.75%	
	No	Cases	13	10	9	9	
		%	81.2%	62.5%	56.2%	56.25%	

The table shows that there was no statistically significant association between smoking and various stages of CKD.

Table 18: HISTORY OF ALCOHOLISM

History of Alcoholism	No. of Patients	Percentage
Yes	16	25
No	48	75
TOTAL	**64**	**100**

Figure 17: HISTORY OF ALCOHOLISM



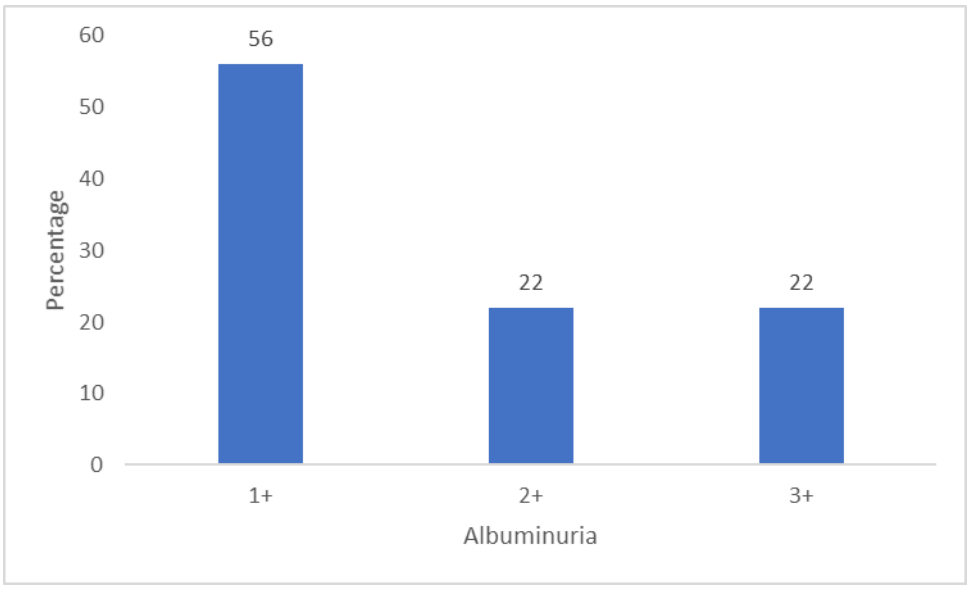
As shown in the table and figure above, only 25 % of patients were alcohol users whereas 75% of the patients did not give history of alcohol intake.

LABORATORY INVESTIGATIONS

Table 19: ALBUMINURIA IN VARIOUS STAGES OF CKD

Albuminuria	No. of Patients	Percentage
1+	36	56
2+	14	22
3+	14	22
TOTAL	**64**	**100**

Figure 18: ALBUMINURIA



As shown in the Table 19 and Figure 18 , 56% of patients had 1+ Proteinuria while 22% each had 2+ and 3+ Proteinuria.

Table 20: HEMOGLOBIN LEVELS IN VARIOUS STAGES OF CKD

Parameter		**Mean**	**Std. Deviation**	**P-Value ANOVA**
HB	CKD Stage I & II	10.8	.8	.004
	Stage III	11.1	1.1	
	Stage IV	11.3	1.0	
	Stage V	9.9	1.6	

As shown in the table above there is a progressive reduction in the haemoglobin level of patients from CKD Stage I to CKD Stage V (10.8±.8 g/dL to 9.9 ± 1.6 g/dL) respectively. This is statistically significant (P=.004).

Table 21: SERUM CHOLESTEROL IN VARIOUS STAGES OF CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
S. CHOLESTEROL	CKD Stage I & II	194.4	26.4	.000
	Stage III	187.1	19.6	
	Stage IV	183.6	7.3	
	Stage V	155.2	13.1	

As shown in the table there is a progressive reduction in the serum cholesterol level from CKD Stage I to Stage V (194.4 $\pm$ 26.4 to 155.2 $\pm$13.1 mg/dL) respectively. This is statistically significant (P=.000).

Table 22: SERUM HDL IN VARIOUS STAGES OF CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
HDL	CKD Stage I & II	36.4	4.0	.002
	Stage III	33.6	3.8	
	Stage IV	29.7	5.3	
	Stage V	32.3	5.4	

As shown in the table there is a significant difference in the HDL levels in various stages of CKD from Stage I to Stage V. The difference is statistically significant (P=.002).

Table 23: SERUM LDL IN VARIOUS STAGES OF CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
LDL	CKD Stage I & II	105.5	16.8	.058
	Stage III	89.8	12.8	
	Stage IV	92.8	19.4	
	Stage V	102.3	22.9	

As shown in the table there is no significant difference (P=.058) in the LDL levels in various stages of CKD from Stage I to Stage V.

Table 24: SERUM VLDL IN VARIOUS STAGES OF CKD

Parameter		**Mean**	**Std. Deviation**	**P-Value ANOVA**
VLDL	CKD Stage I & II	28.6	5.9	.745
	Stage III	27.4	5.3	
	Stage IV	25.9	8.1	
	Stage V	27.9	9.2	

As shown in the table there is no significant difference (P=.745) in the VLDL levels in various stages of CKD from Stage I to Stage V.

Table 25: SERUM ALBUMIN IN VARIOUS STAGES OF CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
S. ALBUMIN	CKD Stage I & II	3.4	.6	.016
	Stage III	3.1	.7	
	Stage IV	2.9	.3	
	Stage V	2.9	.4	

As shown in the table there is a progressive reduction in the serum albumin level from CKD Stage I to Stage V (3.4 ± .6 to 2.9 ± .4 g/L) respectively. This is statistically significant (P=.016).

Table 26: SERUM CALCIUM IN VARIOUS STAGES OF CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
S. CALCIUM	CKD Stage I & II	9.0	.7	.000
	Stage III	9.0	.8	
	Stage IV	7.8	.8	
	Stage V	7.9	.5	

As shown in the table there is a significant difference in the serum calcium levels in various stages of CKD from Stage I to Stage V. The difference is statistically significant (P=.000).

Table 27: SERUM PHOSPHORUS LEVELS IN VARIOUS STAGES OF CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
S. PHOSPHORUS	CKD Stage I & II	3.4	.6	.000
	Stage III	3.4	.5	
	Stage IV	4.4	.5	
	Stage V	5.9	1.2	

As shown in the table there is a progressive increase in the serum phosphorus level from CKD Stage I to Stage V (3.4 ± .6 to 5.9 ± 1.2 mg/dL) respectively. This is statistically significant (P=.000).

Table 28: GLYCOSYLATED HEMOGLOBIN IN VARIOUS STAGES OF CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
HBA1 C MEAN	CKD Stage I & II	6.9	.6	.331
	Stage III	6.7	1.1	
	Stage IV	6.7	1.4	
	Stage V	7.4	1.4	

As shown in the table there is no significant difference (P=.331) in the Glycosylated haemoglobin levels in various stages of CKD from Stage I to Stage V.

2D ECHO MEASUREMENTS

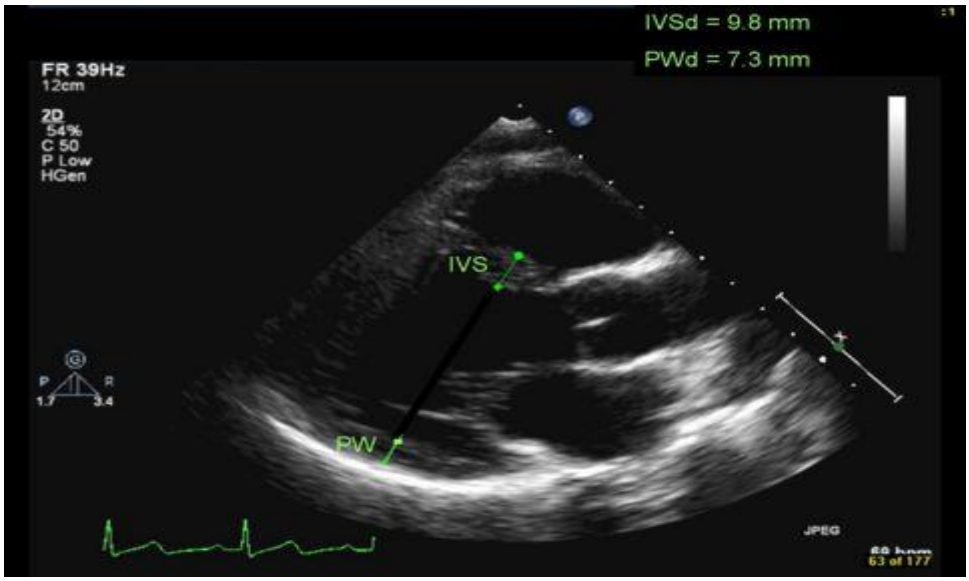
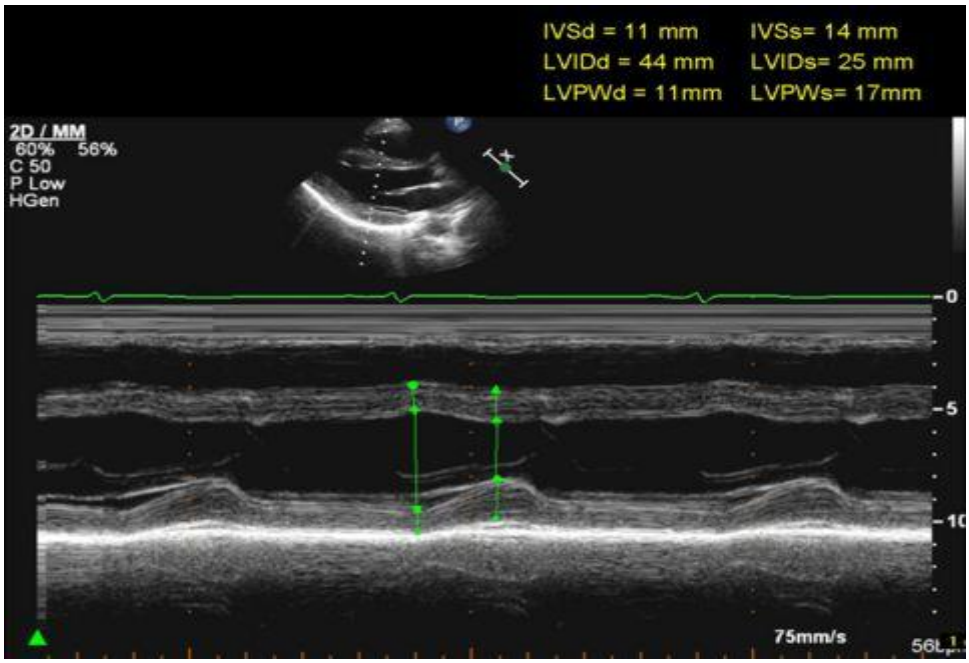


Figure 19: 2D Echocardiogram wall measurements



Figures 20: 2D Echocardiogram wall measurements

Table 29: DESCRIPTIVE DATA OF ECHO CARDIOGRAPHIC FINDINGS

Parameter	Minimum	Maximum	Mean	Std. Deviation
IVS diastolic mm_	8	16	12.95	2.65
IVS systolic mm	10	18	14.90	2.53
LV_Mass_[Grams]	90	299	195.22	65.32
LV_Mass_Index_ [Gram/sq.M]	52	173	112.17	38.83
LV_diameter_Systolic [mm]_	24.8	34	27.11	1.87
LV_diameter_diastolic_[mm]	38	47	42.04	2.43
LA_diameter_[mm]	35	44	37.94	2.40
Posterior Wall diameter [mm]	7	16.4	11.79	2.64
Right Ventricle _diameter_[mm]	25.2	31	27.50	1.37
Pulmonary Artery systolic Pressure [mm Hg]	12	35	20.68	6.71
E/ A	0.64	1.4	0.84	0.17

The Table shows the overall descriptive statistics of various Echocardiographic findings in the cohort.

Table 30: ANALYSIS OF VARIANCE WITH ECHOCARDIOGRAPHIC FINDINGS IN VARIOUS STAGES OF CKD

Parameters	Stage 1 & 2	Stage 3	Stage 4	Stage 5	P value ANOVA
IVSd[mm]	9.5 ± 1.1	12 ± 1.79	14.9 ± 0.64	15.4 ± 0.48	0.000
IVSs[mm]	11.6 ± 0.99	14 ± 1.27	16.5 ± 1.1	17.4 ± 0.34	0.001
LV MASS [gram]	116 ± 19	163 ± 33.5	130 ± 15	161 ± 5.9	0.000
LV s [mm]	25 ± 0.3	26.6 ± 0.8	27.3 ± 1.2	29 ± 2.3	0.001
LVd[mm]	41 ± 1.7	40 ± 1.11	41.6 ± 1.6	45.3 ± 0.79	0.001
L A dia[mm]	36 ± 0.92	36 ± 0.95	37.6 ± 1.4	41.5 ± 1.3	0.000
RV dia[mm]	26.2 ± 0.75	27.4 ± 0.49	27 ± 0.57	29.4 ± 0.96	0.001
E/A	0.84 ± 0.04	0.79 ± 0.03	0.69 ± 0.06	1.03 ± 0.19	0.001

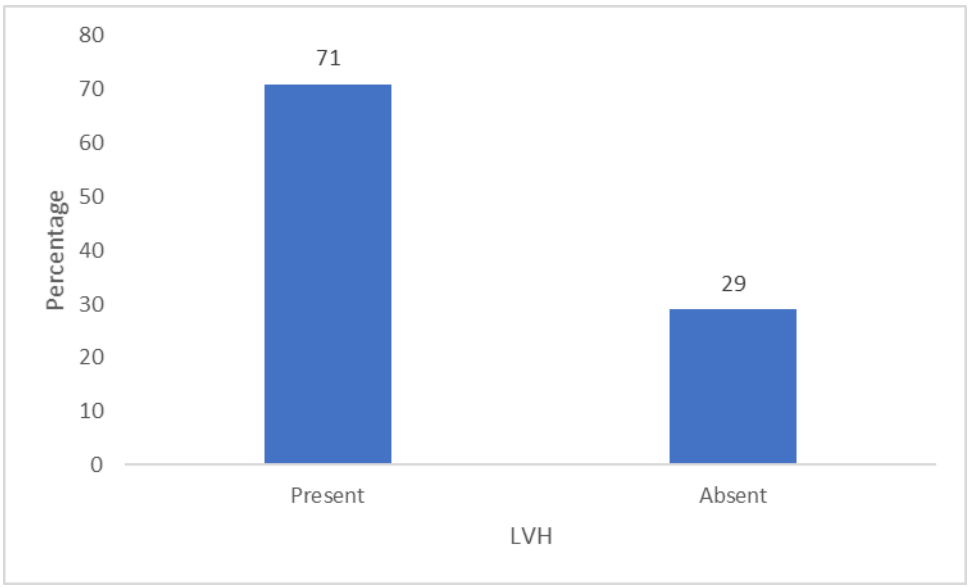
Abbreviations: IVSd= Interventricular Septal thickness Diastolic. IVSs= Interventricular Septal thickness Systolic.LV s= Left Ventricular Systolic thickness. LV d= Left Ventricular Diastolic thickness.LA dia= Left Atrial Diameter. RV dia = Right Ventricular diameter.

There is a progressive increase in the echocardiographic abnormalities from early to late stages of CKD as shown in the Table above. There is a significant increase in Left Ventricular Mass from stage I to Stage V CKD from 116 ± 19 grams to 161 ± 5.9 grams. The Left Atrial Diameter increased significantly from Stage I to Stage V from 36 ± 0.92 mm to 41.5 ± 1.3 mm.

Table 31: LEFT VENTRICULAR HYPERTROPHY(LVH)

LVH	No. of Patients	Percentage
Present	46	71
Absent	18	29
TOTAL	**64**	**100**

Figure 21: LEFT VENTRICULAR HYPERTROPHY(LVH)



In the table and figure above, it is seen that 71% of the patients had Left Ventricular Hypertrophy.

Table 32: ASSOCIATION OF AGE WITH LEFT VENTRICULAR HYPERTROPHY IN CKD

Variable		LVH		P-Value χ^2
		Absent	Present	
Age	< 60	10	34	.071 NS
		52.6%	75.6%	
	> 60	9	11	
		47.4%	24.4%	

As shown in the table above, there is no significant association between Age and Left Ventricular Hypotrophy (P=.071).

Table 33: ASSOCIATION OF GENDER WITH LEFT VENTRICULAR HYPERTROPHY IN CKD

Variable		LVH		P-Value χ^2
		Absent	Present	
GENDER	Male	10	30	.289 NS
		52.6%	66.7%	
	Female	9	15	
		47.4%	33.3%	

As shown in the table there is no significant association between gender and left ventricular hypertrophy (P=.289).

Table 34: ASSOCIATION OF VARIOUS STAGES OF CKD WITH LEFT VENTRICULAR HYPERTROPHY

		LVH		P Value
Groups	CKD 1 & 2	14	2	000 Sig
		77.8%	4.4%	
	CKD 3	4	12	
		22.2%	26.7%	
	CKD 4	0	16	
		0.0%	35.6%	
	CKD 5	0	16	
		0.0%	33.3%	

As shown in the Table, there is a progressive and significant increase in the incidence of Left Ventricular Hypertrophy in various stages of CKD from Stage I to V. This is linked with multiple factors such as salt and water excess, anaemia, hyperparathyroidism, hyperphosphatemia and hypoalbuminemia.

Table 35: ASSOCIATION OF AGE WITH LEFT VENTRICULAR HYPERTROPHY IN CKD

Parameter		Mean	Std. Deviation	P-Value ANOVA
LV MASSINDEX	Group-1	68.3	12.6	.000
	Group-2	89.6	16.5	
	Group-3	132.7	17.6	
	Group-4	161.2	6.1	

There is a significant increase in the left ventricular mass index from Stage I CKD to Stage V CKD with P =.000 shown in the table above.

Table 36: ASSOCIATION BETWEEN ALBUMINURIA GRADES AND LEFT VENTRICULAR HYPERTROPHY

Variable		LVH		P-Value χ^2
		Absent	Present	
ALBUMINURIA	1+	22	14	0.000 Sig.
		64.8%	46.7%	
	2+	11	3	
		32.3%	10.0%	
	3+	1	13	
		2.9%	43.3%	

The Table shows the association between various grades of Albuminuria and Left Ventricular Hypertrophy which is statistically significant (P = 0.000).

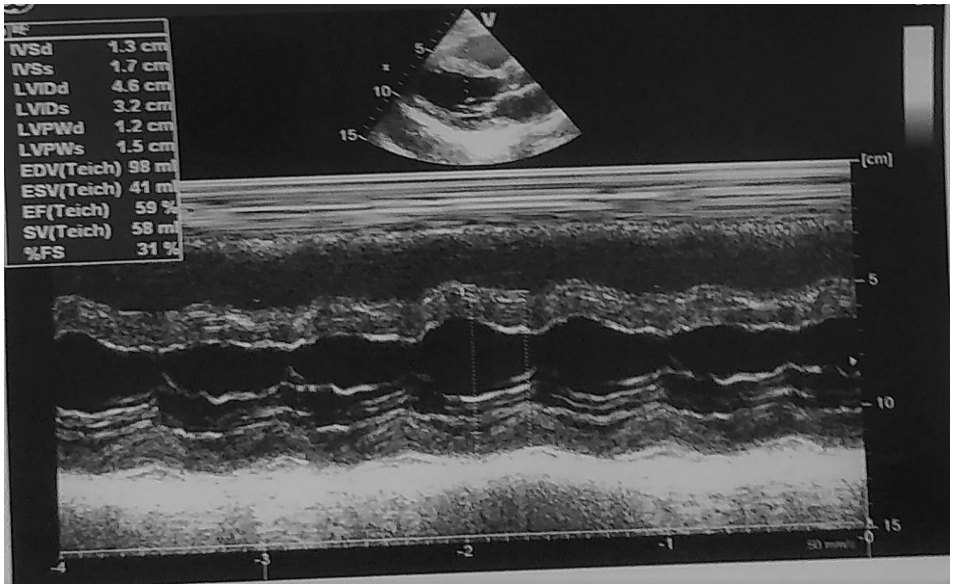


Figure 22: Left Ventricular Hypertrophy in One of the patients

TABLE 37: ASSOCIATION BETWEEN HEMOGLOBIN LEVELS AND LEFT VENTRICULAR HYPERTROPHY

Variable		LVH		P-Value χ^2
		Absent	Present	
HB	< 11	10	30	.001 S
		38.5%	78.9%	
	> 11	16	8	
		61.5%	21.1%	

As shown in the table there is a significant association between haemoglobin and left ventricular hypotrophy (P=.001).

TABLE 38: ASSOCIATION BETWEEN SMOKING AND LEFT VENTRICULAR HYPERTROPHY

Variable		LVH		P-Value χ^2
		Absent	Present	
SMOKING	Yes	4	19	.152 NS
		22.2%	41.3%	
	No	14	27	
		77.8%	58.7%	

As shown in the table above there is no significant association between Smoking and Left Ventricular Hypotrophy (P=.152).

Table 39: ASSOCIATION BETWEEN ALCOHOLISM AND LEFT VENTRICULAR HYPERTROPHY

Variable		LVH		P-Value χ^2
		Absent	Present	
ALCOHOLISM	Yes	4	13	.622 NS
		22.2%	28.3%	
	No	14	33	
		77.8%	71.7%	

As shown in the table there is no significant association between Alcoholism and Left Ventricular Hypotrophy (P=.622).

TABLE 40: ASSOCIATION BETWEEN HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

Variable		LVH		P-Value χ^2
		Absent	Present	
HYPERTENSION	Yes	10	39	.003 Sig
		52.6%	86.7%	
	No	9	6	
		47.4%	13.3%	

As shown in the table there is a significant association between Hypertension and Left Ventricular Hypotrophy (P=.003).

TABLE 41: ASSOCIATION BETWEEN DIABETES AND LEFT VENTRICULAR HYPERTROPHY

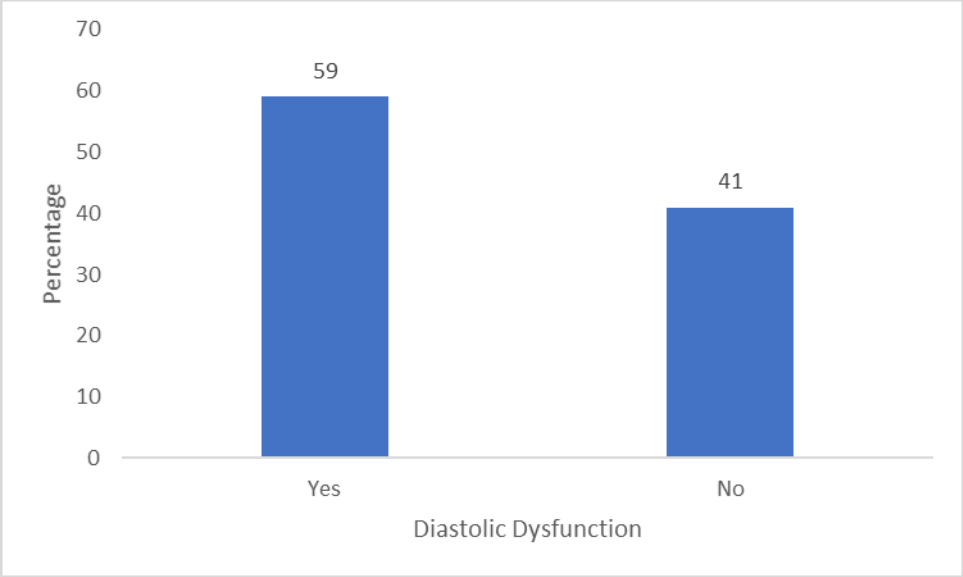
Variable		LVH		P-Value χ^2
		Absent	Present	
DIABETES	Yes	13	23	.202 NS
		68.4%	51.1%	
	No	6	22	
		31.6%	48.9%	

As shown in the table above, there is no significant association between Diabetic status and Left Ventricular Hypotrophy (P=.202).

Table 42: DIASTOLIC DYSFUNCTION

Diastolic Dysfunction	No. of Patients	Percentage
Yes	38	59
No	26	41
TOTAL	**64**	**100**

Figure 23: DIASTOLIC DYSFUNCTION



As shown in the Figure above 59% of patients showed evidence of Diastolic dysfunction of the Left Ventricle.

Table 43: ASSOCIATION BETWEEN DIASTOLIC DYSFUNCTION AND CKD STAGES

			CKD STAGES				P-Value χ^2
			Stage I & II	**Stage III**	**Stage IV**	**Stage V**	
DIASTOLIC DYSFUNCTION	Present	Cases	5	6	11	16	.000
		%	31.2%	37.5%	68.8%	100.0%	
	Absent	Cases	11	10	5	0	
		%	68.8%	62.5%	31.2%	0.0%	

As shown in the Table, there is a significant association between stages of CKD and Diastolic Dysfunction. The incidence increases from 31% in Stage I to 100% in Stage V of CKD.

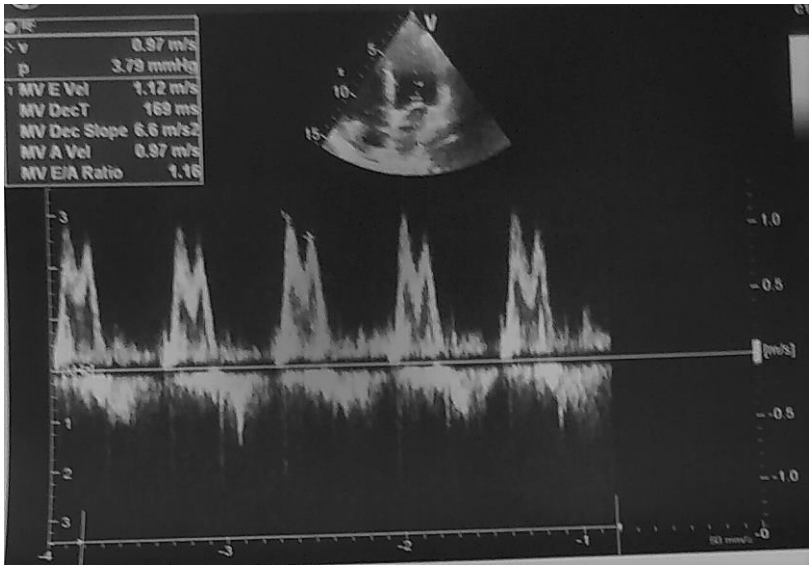
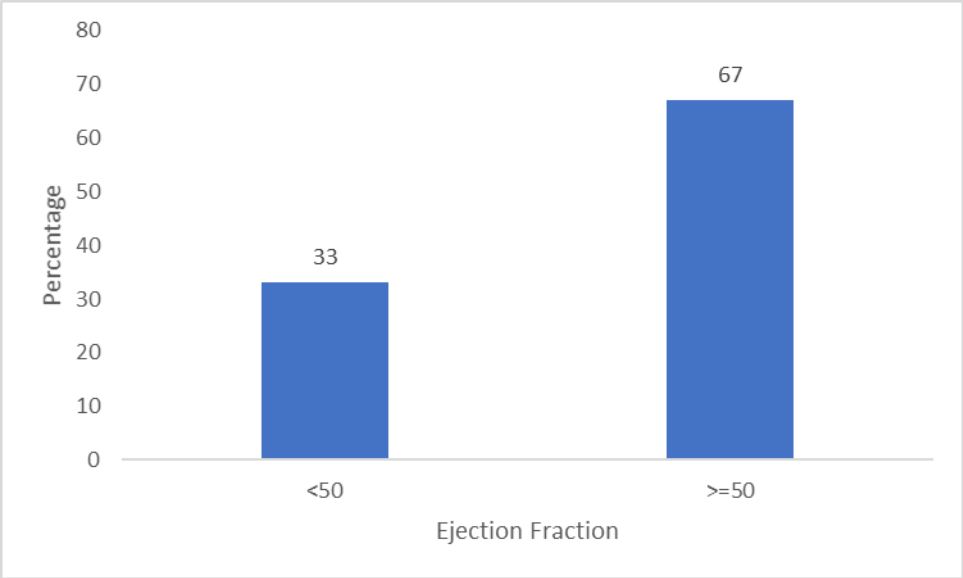


Figure 24 : Grade II Diastolic Dysfunction in one of the Patients

Table 44: EJECTION FRACTION IN CKD

Ejection Fraction	No. of Patients	Percentage
<50	21	33
>=50	43	67
TOTAL	**64**	**100**

Figure 25: EJECTION FRACTION



The figure shows that systolic dysfunction in the form of reduced Ejection Fraction below 50% was encountered in 33% of patients while 67% of patients had a normal Ejection Fraction.

Table 45: ASSOCIATION BETWEEN EJECTION FRACTION AND CKD STAGES

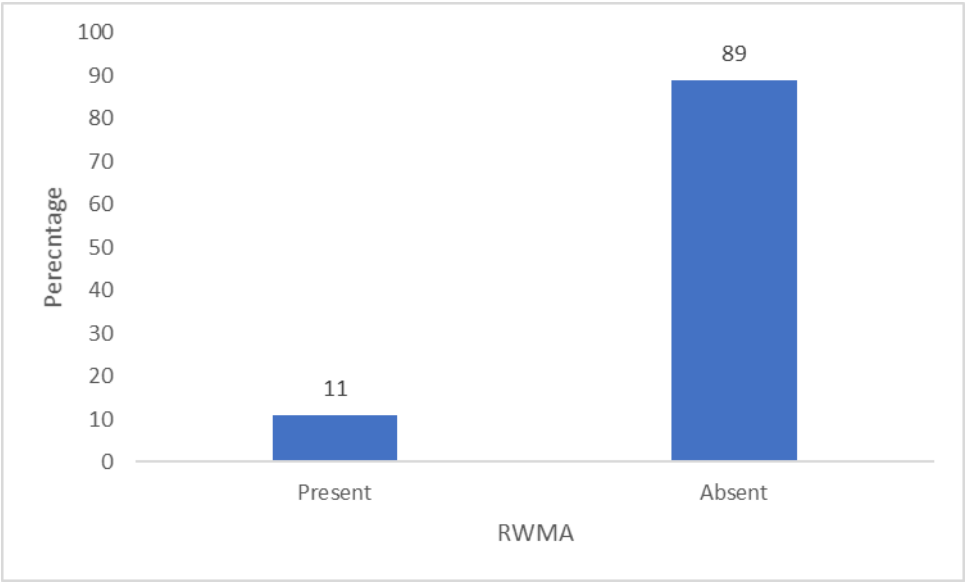
			CKD STAGES				P-Value χ^2
			Stage I & II	Stage III	Stage IV	Stage V	
EF	< 50	Cases	3	6	6	6	.625
		%	18.8%	37.5%	37.5%	37.5%	
	> =50	Cases	13	10	10	10	
		%	81.2%	62.5%	62.5%	62.5%	

As shown in the Table there is no statistically significant Association between various stages of CKD and grades of Ejection fraction.

Table 46: REGIONAL WALL MOTION ABNORMALITY(RWMA) IN CKD

RWMA	No. of Patients	Percentage
Present	7	11
Absent	57	89
TOTAL	**64**	**100**

Figure 26: REGIONAL WALL MOTION ABNORMALITY(RWMA) IN CKD

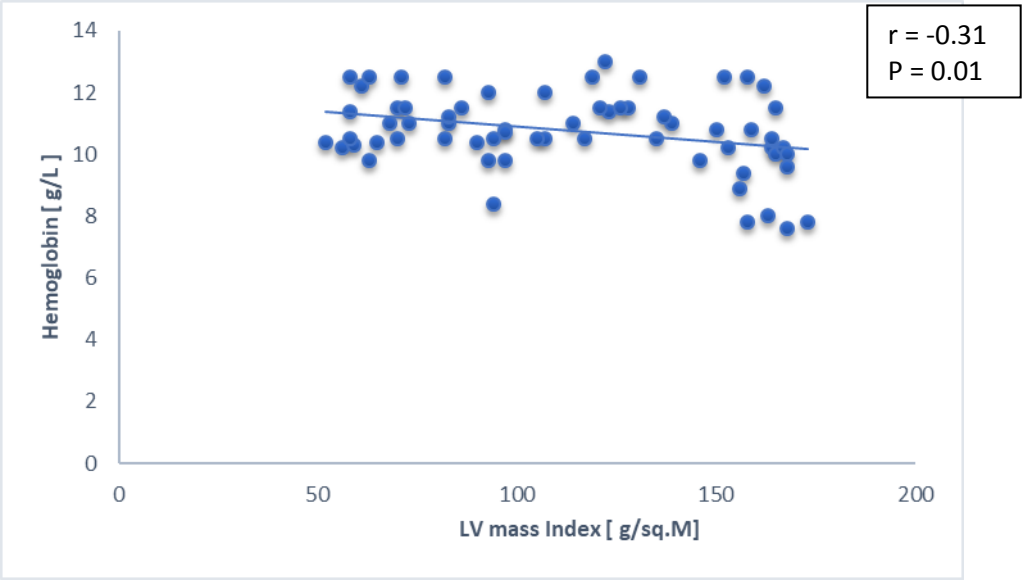


As shown in the Figure Regional Wall motion abnormalities are seen in 11% of patients.

Figure 27: CORRELATION BETWEEN LV MASS INDEX AND ESTIMATED GFR

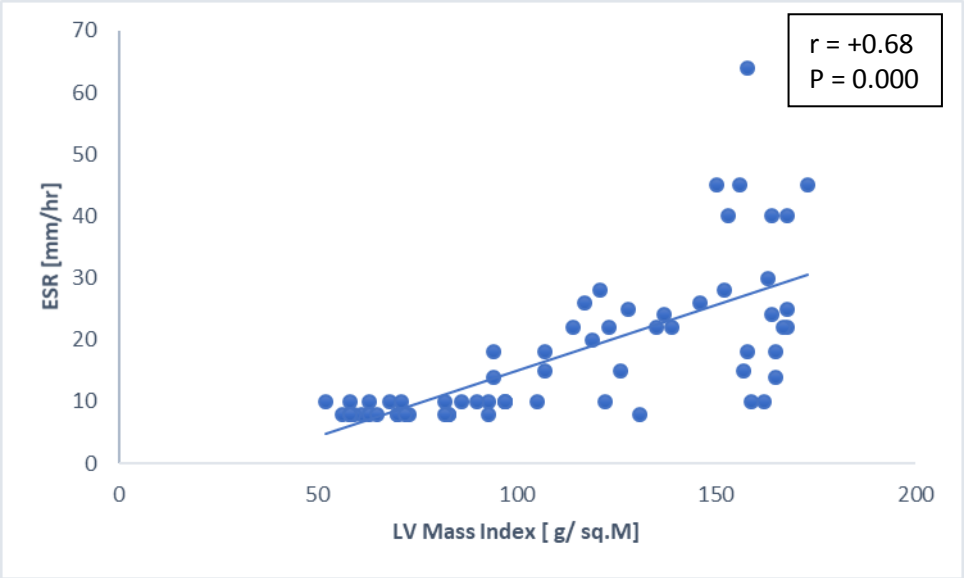
The graph above shows the strong negative relationship between estimated GFR and LV mass Index with r = -0.89. It is statistically significant with P=< 0.001.

Figure 28: CORRELATION BETWEEN LV MASS INDEX AND HAEMOGLOBIN



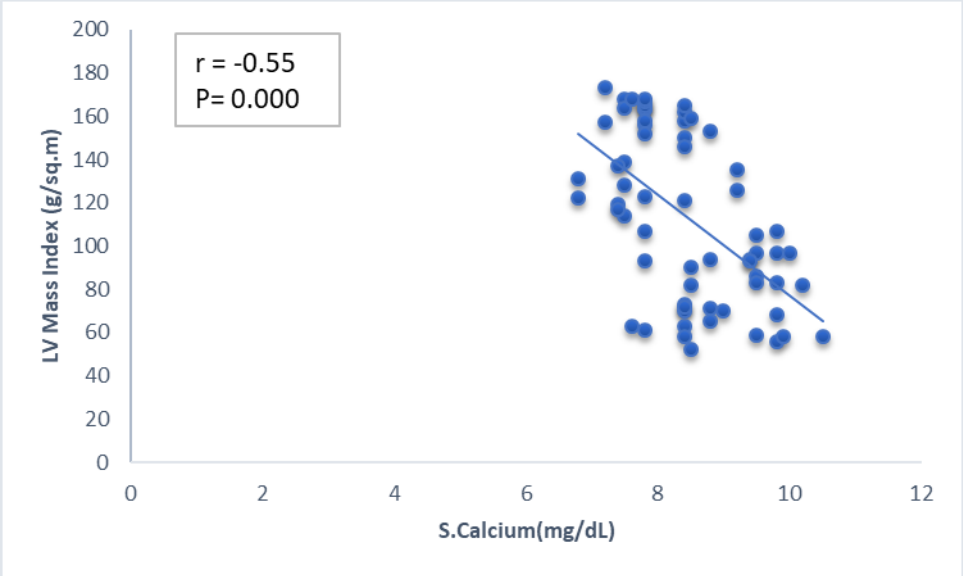
The graph shows a weak negative relationship between haemoglobin levels and LV mass Index with a r value of -0.31. The P value of 0.01.

Figure 29: CORRELATION BETWEEN LV MASS INDEX AND ESR



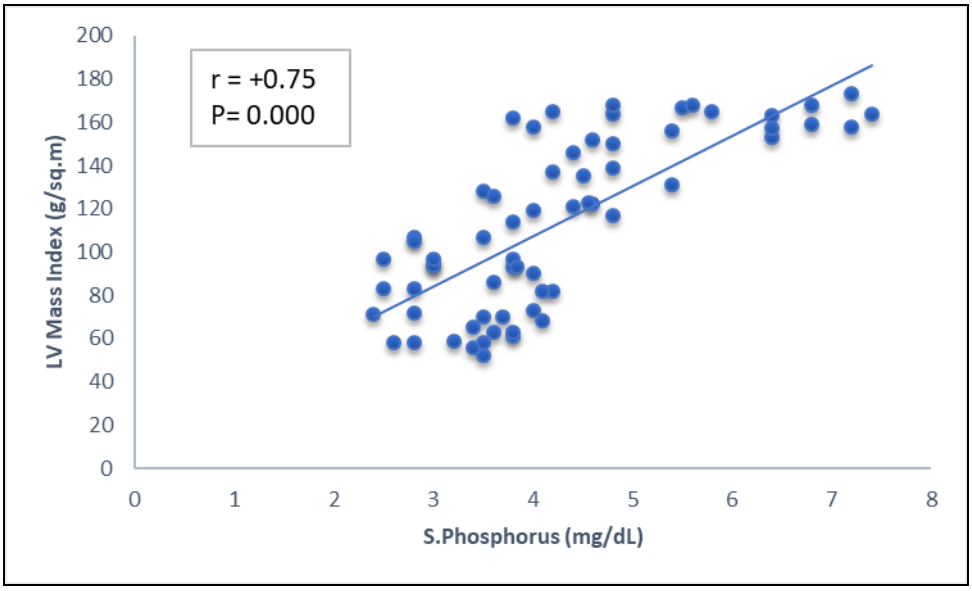
The graph shows a strong positive correlation between ESR and LV Mass Index with a r value of + 0.68. This is statistically highly significant with P value of 0.000.

Figure 30: CORRELATION BETWEEN LV MASS INDEX AND SERUM CALCIUM



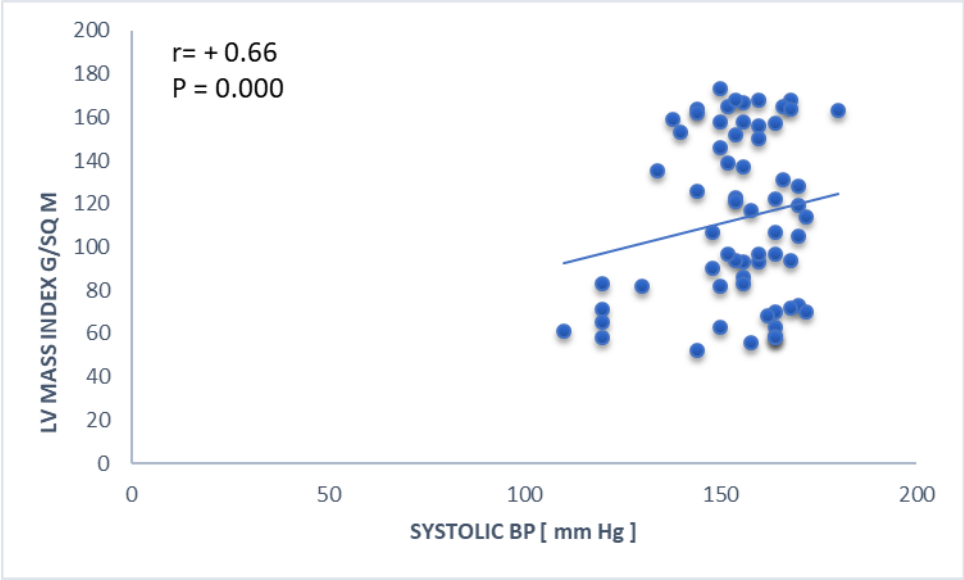
The graph above depicts a moderate negative relationship with r = -0.55 between serum calcium levels and LV mass Index. The P value was 0.000.

Figure 31: CORRELATION BETWEEN LV MASS INDEX AND SERUM PHOSPHORUS



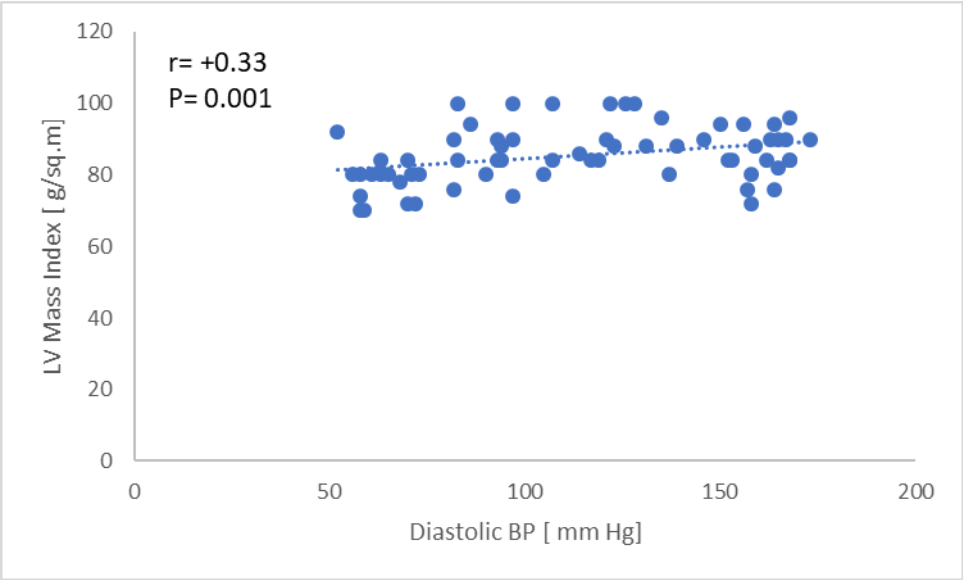
The graph shown above reveals a highly significant Positive correlation of + 0.75 between serum Phosphorus levels and LV mass Index with a P value of 0.000.

Figure 32: CORRELATION BETWEEN LV MASS INDEX AND SYSTOLIC BP



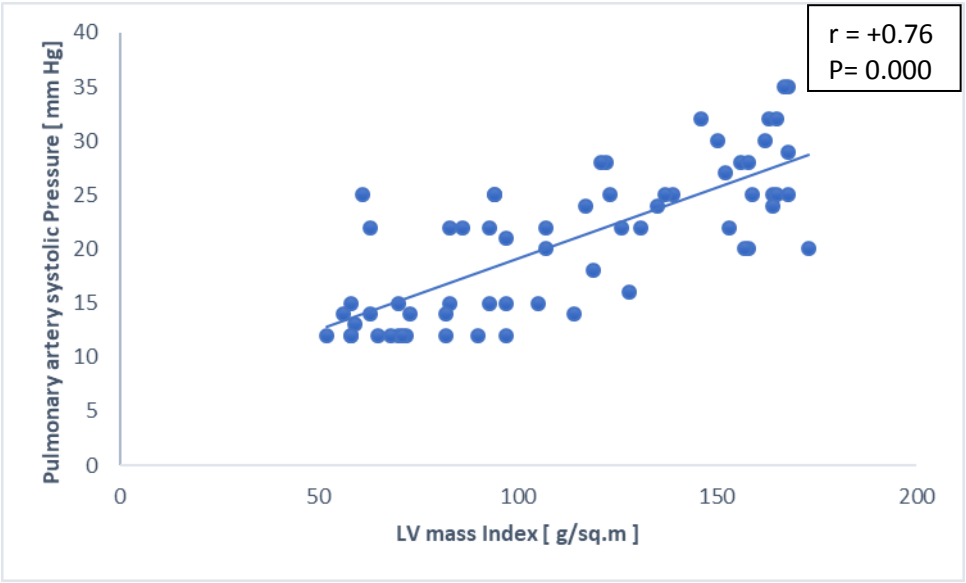
The graph shown above represents a strong positive correlation of +0.66 between Systolic Blood Pressure and LV Mass Index. It was statistically significant with a P value of 0.000.

Figure 33: CORRELATION BETWEEN LV MASS INDEX AND DIASTOLIC BP



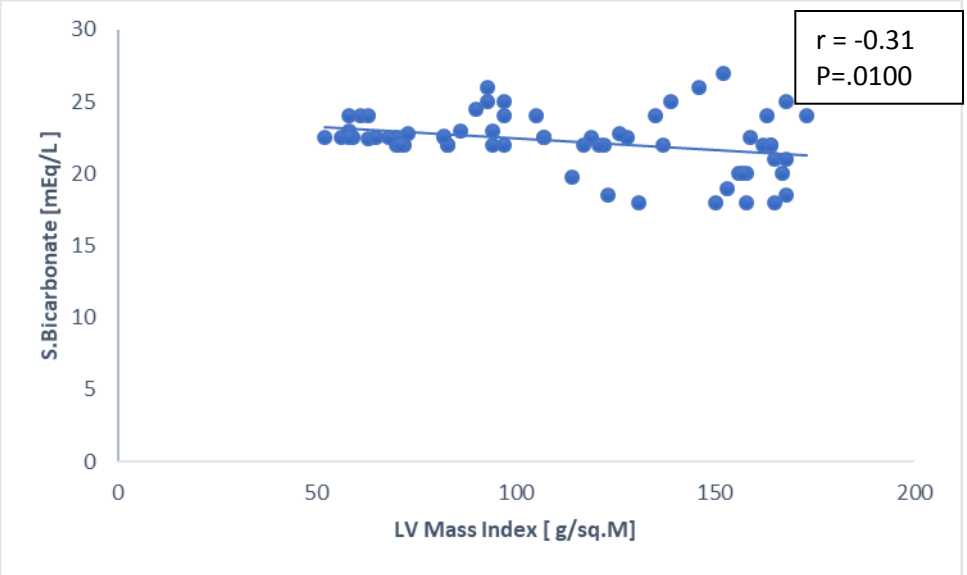
The graph shown above represents the weak positive correlation of + 0.33 between LV mass index and Diastolic Blood Pressure with a significant P value of 0.001.

Figure 34: CORRELATION BETWEEN LV MASS INDEX AND PULMONARY HYPERTENSION



The figure 5.20 shows the high correlation of Pulmonary Hypertension and Left ventricular mass Index.

Figure 35: CORRELATION BETWEEN LV MASS INDEX AND SERUM BICARBONATE



The Figure 5.21 shows moderate Negative correlation of serum Bicarbonate with LV Mass Index with a r value of -0.31. It is statistically significant with P value of 0.01.

Table 47: MULTIPLE REGRESSION ANALYSIS OF VARIOUS RISK FACTORS

LINKED TO LV MASS INDEX

Parameters	Coefficients	Standard Error	t Stat	P-value
eGFR*	-0.990	0.117	-8.444	0.000*
S.ALBUMIN	-3.741	3.869	-0.967	0.338
S.CALCIUM	1.546	2.819	0.548	0.586
S.PHOSPHOROUS*	8.090	2.425	3.336	0.0028*
HEMOGLOBIN	-2.457	1.811	-1.357	0.180
S. BICARBONATE	0.771	1.094	0.705	0.484
Systolic BP	0.070	0.147	0.478	0.634
Diastolic BP	-0.199	0.306	-0.651	0.518

A multiple regression analysis taking LV mass Index as dependent variable and Multiple non traditional risk factors such as Estimated GFR, Serum Albumin, Serum calcium, Serum Phosphorus , Hemoglobin and Serum Bicarbonate was carried out . It can seen from the Table above that Estimated GFR and serum Phosphorus levels showed a statistically significant association enabling prediction of LV mass Index.

DISCUSSION

DISCUSSION

In this prospective study we analysed subclinical echocardiographic abnormalities in CKD and the link between various traditional and non traditional risk factors in the causation of cardiovascular events in CKD.

Age is a traditional risk factor for cardiovascular disease in CKD. In our study more than 40% of the cohort of patients were aged above 60 years. In the Framingham offspring cohort study it was found that age and cardiovascular disease were positively correlated in CKD patients as shown by Parikh et al.[146]. The mean age of our cohort was 58 $\pm$ 5 years where as in the Indian CKD registry the mean age was reported as 50 years $\pm$ 14 years as shown by Rajapurkar et al [147].

The Gender based prevalence of CKD is similar to data from CKD Registry of India where a 70; 30 pattern of male; female incidence of Chronic Kidney disease was shown by Rajapurkar et al .[147]Gender differences exist in various diagnostic categories of CKD such as Hypertensive nephrosclerosis and glomerulonephritis where male predominance is seen. In diseases such as Systemic Lupus Erythematosus, female predominance is common.

Diabetic Nephropathy is the commonest cause of CKD in Indian Population in the CKD Registry as shown by Rajapurkar et al.[147]. More than 30% of Type 2 Diabetic patients are at risk of developing CKD and being a diabetic is a coronary risk equivalent[147].

Hypertension a traditional risk factor for cardiovascular disease in CKD. Progression of CKD and Major cardiovascular events are strongly related to Blood Pressure in CKD Patients as shown in the UKPDS study. Adler et al, have shown that for every 10 mm Hg reduction in Blood Pressure , there was a 15% reduction in risk related to all cause and cardiovascular mortality.[148] Intensive Blood Pressure lowering reduces the Major cardiovascular events in CKD patients. Lv Jicheng et al., have shown that hypertension is resistant in CKD requiring multiple drugs to reduce it to Goal Blood Pressure [149]

CKD patients show higher cardiovascular mortality with lower BMI and malnutrition. This trend is known as the reverse epidemiology where obesity is shown to be a protective factor for survival of dialysis patients. Kamyar Kalantar-Zadeh et al., have shown that obesity is a protective factor to improve survival in dialysis patients. [150] The proposed hypothesis implicates several factors such as better nutrition and anti-endotoxin action of lipoproteins.

Smoking is a major risk factor for both acceleration of progression of CKD and cardiovascular disease. Nakamuro et al., have shown that the hazard ratios in male current smokers with CKD were 2.26 for all-cause mortality and 2.66 for cardiovascular diseases, respectively[151].

The link between alcohol use and CKD is controversial with evidences both for and against. Cheungpastiporn et al, have shown in a meta - analysis an inverse association between alcohol consumption and risk of development of CKD in males[152].

Albuminuria is a non - traditional risk factor for cardiovascular morbidity in CKD. McQuirre et al have shown that albuminuria is independently and significantly associated with left ventricular mass in patients with CKD in a study involving cardiac MRI. This relationship was independent of blood pressure thus highlighting a non-traditional risk between CKD cardiovascular disease[153].

CRP is a marker of inflammation and various studies have correlated high CRP levels with inflammation and cardiovascular disease in CKD. Georgi Abraham et al., have shown that elevated CRP was elevated in 67% of patients in the CKD cohort. It was correlated with low serum albumin levels, anemia and Diabetic status[154].

ESR is a known a surrogate marker of Inflammation. In our study high ESR positively correlated with LV mass Index.

In the study by Ladda et al., Left ventricular hypertrophy was seen in 71% of patients OF CKD by echocardiogram[155]

When Doppler flow signals are obtained from the mitral annulus during diastole, 4 distinct phases could be delineated. Phase 1 denotes the Isovolemic relaxation. Phase 2 denotes the Early filling phase. Upto 70-85% of Left ventricular filling occurs during this phase. The tissue doppler velocity at this phase is denoted by E in the dopplewr recordings. Phase 3 is the diastatsis. In the 4 th phase, atrial contraction where upto 15-20% of LV filling occurs. The E/A ratio is a marker of diastolic function of the left ventricle of the heart.

It represents the ratio of peak velocity blood flow from gravity in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave). When the LV diastolic function is normal, E > A. In Grade 1 Diastolic Dysfunction the atrial flow velocity is more than early filling velocity at the mitral annulus thus showing a E< A pattern. In Grade 2 Diastolic Dysfunction, a pseudonormal pattern develops where E: A is apparently normal. However, by pulmonary vein pulse wave doppler, it can be shown that the relaxation pattern is abnormal (systolic blunting, a decrease in the height of the S wave). In addition, performance of a valsalva manoeuvre will result in unmasking of the pseudonormal state.In Grade 3 Diastolic Dysfunction denoted as restrictive filling , E:A is > 2. Ali Ahmed et al., have shown that Diastolic dysfunction is a better marker than Systolic dysfunction for predicting mortality in CKD patients[156]. In the study conducted on Indian patients, Laddha et al., has shown that systolic and diastolic dysfunction were seen in 24% and 61% of patients with CKD respectively[155]. Both systolic and Diastolic cardiac dysfunction are associated with worsening levels of CKD as shown in our study which is similar to study carried out by Ahmed et al. [156].

Andrew House et al., have shown that more than 40% of patients with advanced CKD have heart failure which is manifested as reduced ejection fraction [157].

Regional wall motion abnormalities are common in CKD patients on hemodialysis. This phenomenon is called myocardial stunning and is the forerunner to uremic cardiomyopathy characterised by reduced cardiac systolic function as described by A.Covic et al [158]

In the analysis of Chronic Renal insufficiency cohort by Navaneethan et al., Pulmonary artery hypertension is associated Left Ventricular hypertrophy. It was associated with higher risk of death and cardiovascular events. In our study, there was a highly significant correlation of Pulmonary arterial systolic Pressure and LV mass Index[159].

Anemia is a non - traditional risk factor for cardiovascular morbidity in CKD patients. Adeera Levin has explained the pathophysiologic link between anemia and Left ventricular hypertrophy[160].

A study conducted in Taiwan by Chang et al., enrolled 415 patients for longitudinal follow up. It showed that co - existence of anemia and LVH independently predicted faster GFR decline and worse cardiovascular prognosis[161].

There is a progressive and significant increase in the incidence of Left Ventricular Hypertrophy in various stages of CKD from Stage I to V. This is linked with multiple factors such as salt and water excess, anemia, hyperparathyroidism, hyperphosphatemia and hypoalbuminemia.

Similar to our study which showed a positive association between Left ventricular mass and calcium Phosphorus abnormalities, Sonkar et al., studied the impact of serum levels of calcium Phosphorus levels on the cardiac function in CKD patients. Diastolic dysfunction was present in 48.8% of the cases and was significantly associated with serum phosphorus and calcium-phosphorous product, but not with Vitamin D level.

They concluded that Hyperphosphatemia and high calcium-phosphorous product can be a better early predictor of diastolic dysfunction than Vitamin D while secondary hyperparathyroidism with increased Left Ventricular Mass may be a bad prognostic marker[162]. Hyperphosphatemia is linked to left ventricular hypertrophy and dysfunction in various stages of CKD in multiple studies [163,164,165,166].

In our study Serum Bicarbonate was negatively correlated with LV mass Index. In the longitudinal follow up of elderly CKD population Dobre et al., found that high rather than low serum bicarbonate levels were associated with cardiovascular mortality[167].

Major et al., recently conducted a meta-analysis of non-traditional risk factors in cardiovascular events in CKD. The review of 27,465 individuals and 100,838 person-years it was revealed that in addition to established traditional general population cardiovascular risk factors, left ventricular hypertrophy, serum albumin, phosphate, urate and hemoglobin were all found to be statistically significant in their association with future cardiovascular events[168]. These findings are in agreement with our study findings.

SUMMARY
AND
CONCLUSION

SUMMARY

We performed a Prospective Observational study of various traditional and non-traditional cardiovascular risk factors in CKD and their impact on echocardiographic measurements of cardiac function.

- The mean age of our cohort was 46 years ± 5 years. 60% of the patients were below the age of 60 years whereas 40% were above the age of 60 years.
- Men constituted 63% of the study population while females constituted 27%.
- The mean Body Mass Index was 22 ± 2.4.
- 56% of the patients were diabetics and 76% were hypertensives.
- 36% were smokers and 25% consumed alcohol regularly.
- 54% of patients had low Hemoglobin levels below 11 %.
- Only 14% were having hypercholesterolemia highlighting reverse causality of low cholesterol levels with higher cardiovascular mortality in late stages of CKD.
- Only 1.5 % of patients were shown to have high LDL levels above 125 mg /d L again pointing towards the role of malnutrition in cardiovascular pathogenesis.
- 65% of the patients were having low HDL levels.
- Serum albumin levels were less than 3 g/ d L in 60% of patients with Protein Energy Wasting and higher risk of CV morbidity and mortality.

- 22% were with Nephrotic range proteinuria which is again a major non-traditional risk factor.

- Diastolic dysfunction was a major Subclinical Echocardiographic finding in 31% of Stage I CKD and 100% of Stage V CKD.
- Systolic dysfunction was seen in 18% of CKD Stage I patients and 37% of Stage V CKD patients.
- LVH was seen in 71 % of patients constituting a heavy burden of cardiovascular events in this cohort.
- The following had positive association with LVH. Traditional risk factors such as High systolic BP, Diabetic status and Smoking status .
- Non-traditional risk factors such as Estimated GFR, ESR, Anemia, Albuminuria, hyperphosphatemia, Hypocalcemia, Metabolic acidosis and elevated C-Reactive Protein were shown to be significantly associated with Left Ventricular Mass Index by Univariate analysis.
- In Multivariate analysis , it was shown that Estimated GFR and Hyperphosphatemia were significant predictors of Left ventricular Mass Index.

CONCLUSION

It has been observed that subclinical echocardiographic abnormalities are common in CKD patients. Both traditional and many potentially modifiable Non-traditional risk factors have shown significant correlation with several Echocardiographic abnormalities.

In our study we found that Hypertension, Anemia , Estimated GFR, Serum calcium, Phosphorus levels and Albuminuria were such factors. These have to be addressed at multiple levels by Blood Pressure Control, Iron and Erythropoietin therapy for anemia, Phosphate restriction and Phosphate binders, correction of anemia with both Iron and Erythropoietin supplements and Lastly reducing the Inflammatory status of High CRP levels with regular dialysis. It can be concluded that the cardiovascular Prognosis can be considerably improved if such multi-pronged approach is undertaken to address the risk factors from an early stage of CKD.

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BIBLIOGRAPHY

BIBLIOGRAPHY

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY*:* Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization.*N Engl J Med* 2004; 351: 1296–1305.

2. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J*:* Reduced kidney function as a risk factor for incident heart failure: The atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* 2007; 18*:*1307–1315.

3. Paoletti E , Bellino D , Cassottana P , Rolla D , Cannella G : Left Ventricular Hypertrophy in non diabetic Predialysis CKD . AmJKidneyDis 2005;46 : 320-327

4. C. deFilippi, S. Wasserman, S. Rosanio, E. Tiblier, H. Sperger, M. Tocchi, *et al.*Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis JAMA 2003; 290: 353–359

5. M. Goicoechea, S.G. de Vinuesa, F. Gomez-Campdera, J. Luno Predictive cardiovascular risk factors in patients with chronic kidney disease (CKD) Kidney Int Suppl 2005; 93:S35–S38

6. Levey AS, de Jong PE, Coresh J, et al. The definition, classification,and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17-28

7. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010;303(5):423

8. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. [online] Available from http://www.kidney.org/professionals/kdoqi/guidelines ckd/p4 class g3.htm

9. Sicree R, Shaw J, Zimmet P. Diabetes and impaired glucose tolerance. In: Gan D (Ed). Diabetes Atlas, 3rd edition. Brussels: International Diabetes Federation; 2006. pp. 15-109

10. Agarwal SK, Dash SC, Irshad M, et al. Prevalence of chronic renal failure in adults in Delhi, India. Nephrol Dial Transplant. 2005;20(8):1638-42.

11. Mani MK. Prevention of chronic renal failure at the community level. Kidney Int Suppl. 2003;63(83):S86-9.

12. Mani MK. Experience with a program for prevention of chronic renal failure in India. Kidney Int Suppl. 2005;67(94):S75-8.

13. Agarwal SK, Dash SC, Irshad M, et al. Prevalence of chronic renal failure in adults in Delhi, India. Nephrol Dial Transplant. 2005;20(8):1638-42.

14. Modi GK, Jha V. The incidence of end-stage renal disease in India: a population-based study. Kidney Int. 2006;70(12):2131-3

15. Schwenger V, Müssig C, Hergesell O, et al. Incidence and clinical characteristics of renal insufficiency in diabetic patients. Dtsch Med Wochenschr. 2001;126(47):1322-6

16. Guideline 11: KDOQI Clinical Practice Guidelines on HypertensionAnd Antihypertensive Agents in Chronic Kidney Disease. [online] Available from http://www.kidney.org/professionals/kdoqi/guidelines_bp/index.htm.[Accessed eptember, 2012].

17. CKD registry of India: Indian Society of Nephrology. [online] Available from http://www.ckdri.org

18. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32: S112-S119 [PMID: 9820470]

19. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000; 356: 147-152 [PMID: 10963260 DOI: 10.1016/S0140-6736(00)02456-9]

20. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R,Kaufman A, Lewis J, Rocco M, Toto R, Windus D, Ornt D, Levey AS. Cardiac diseases in maintenance hemodialysis patients: resultsof the HEMO Study. Kidney Int 2004; 65: 2380-2389 [PMID:15149351 DOI: 10.1111/j.1523-1755.2004.00657.x]

21. Jardine AG, Gaston RS, Fellstrom BC, Holdaas H. Prevention of cardiovascular disease in adult recipients of kidney transplants. Lancet 2011; 378: 1419-1427 [PMID: 22000138 DOI: 10.1016/S0140-6736(11)61334-2]

22. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351: 1296-1305 [PMID: 15385656 DOI: 10.1056/NEJMoa041031]

23. Moran, A., Katz, R., Jenny, N. S., et al. (2008). Left ventricular hypertrophy in mild and moderate reduction in kidney function determined using cardiac magnetic resonance imaging and cystatin C: the multi-ethnic study of atherosclerosis (MESA). Am J Kidney Dis, 52(5), 839–48.

24. Nardi, E., Palermo, A., Mulè, G., et al. (2009). Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease. J Hypertens, 27(3), 633–41.

25. Eckardt, K. U., Scherhag, A., Macdougall, I. C., et al. (2009). Left ventricular geometry predicts cardiovascular outcomes associated with anaemia correction in CKD. J Am Soc Nephrol, 20(12), 2651–60.

26. Tucker, B., Fabbian, F., Giles, M., *et al.* (1997). Left ventricular hypertrophy and ambulatory blood pressure monitoring in chronic renal failure. *Nephrol Dial Transplant*, 12(4), 724–8.

27. Paoletti, E., Bellino, D., Cassottana, P., et al. (2005). Left ventricular hypertrophy in nondiabetic predialysis CKD. Am J Kidney Dis, 46(2), 320–7.

28. Park, M., Hsu, C. Y., Li, Y., et al. (2012). Associations between kidney function and subclinical cardiac abnormalities in CKD. J Am Soc Nephrol,
(10), 1725–34.

29. Paoletti, E., Bellino, D., Gallina, A. M., et al. (2011). Is left ventricular hypertrophy a powerful predictor of progression to dialysis in chronic kidney disease Nephrol Dial Transplant, 26(2), 670–7.

30. Hayashi, S. Y., Rohani, M., Lindholm, B., *et al.* (2006). Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging. *Nephrol Dial Transplant*, 21(1), 125–32

31. Beata Franczyk-Skóra, Anna Gluba, Robert Olszewski, Maciej Banach, Jacek Rysz Heart function disturbances in chronic kidney disease – chocardiographic indices. Arch Med Sci 2014; 10, 6: 1109–1116

32. Agarwal S, Dangri P, Kalra OP, Rajpal S. Echocardiographic assessment of cardiac dysfunction in patients of chronic renal failure. JIACM 2003; 4: 296-303.

33. Hayashi SY, Rohani M, Lindholm B, et al. Left ventricular function in patients with chronic kidney disease evaluated by colour tissue Doppler velocity imaging. Nephrol Dial Transplant 2006; 21: 125-32.

34. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. BMJ 2010;341:c4986.

35. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology
and Prevention. Circulation 2003;108:2154–69.

36. Keller CK, Bergis KH, Fliser D, Ritz E. Renal findings in patients with short-term type 2 diabetes. J Am Soc Nephrol 1996;7:2627–35.

37. Raj DS, Choudhury D, Welbourne TC, Levi M. Advanced glycation end products: a nephrologist's perspective. Am J Kidney Dis 2000;35:365–80.

38. Ruggenenti P, Fassi A, Ilieva AP, et al. on behalf of the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941–51.

39. Patel A, MacMahon S, Chalmers J, et al. on behalf of the ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–40.

40. Makino H, Haneda M, Babazono T, et al. on behalf of the INNOVATION Study Group. Prevention of transition from incipient to overt nephropathy with telmisartan in patients with type 2 diabetes. Diabetes Care 2007;30:1577–8.

41. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation 2007; 116: 85-97 [PMID: 17606856 DOI: 10.1161/CIRCULATIONAHA. 106.678342]

42. Kaysen GA. Potential restoration of HDL function with apolipoprotein A-I mimetic peptide in end-stage renal disease. Kidney Int 2009; 76: 359-361 [PMID: 19644477 DOI:10.1038/ki.2009.205]

43. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Semin Dial 2003;16:101–5.

44. Shoji T, Nishizawa Y. Plasma lipoprotein abnormalities in hemodialysis patients—clinical implications and therapeutic guidelines. Ther Apher Dial 2006;10:305–15.

45. Apostolov EO, Basnakian AG, Ok E, Shah SV. Carbamylated low-density lipoprotein: nontraditional risk factor for cardiovascular events in patients with chronic kidney disease. J Ren Nutr 2012;22:134–8.

46. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395–407.

47. Hou W, Lv J, Perkovic V, *et al.* Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta analysis. Eur Heart J 2013;34:1807–17.

48. Hou W, Lv J, Perkovic V, *et al.* Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and metaanalysis. Eur Heart J 2013;34:1807–17.

49. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E. Renal function in the elderly: impact of hypertension and cardiac function. Kidney Int 1997;51:1196–204.

50. Farmer CK, Goldsmith DJ, Cox J, Dallyn P, Kingswood JC, Sharpstone P. An investigation of the effect of advancing uraemia, renal replacement therapy and renal transplantation on blood pressure diurnal variability.
Nephrol Dial Transplant 1997;12:2301–7.

51. Buckalew VM Jr, Berg RL, Wang SR, Porush JG, Rauch S, Schulman G. Prevalence of hypertension in 1,795 subjects with chronic renal disease: the Modification of Diet in Renal Disease Study baseline cohort. Modification of Diet in Renal Disease Study Group. Am J Kidney Dis 1996;28:811–21.

52. Dis 1996;28:811–21.39 Klassen PS, Lowrie EG, Reddan DN, et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. JAMA 2002;287:1548–55.

53. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. Hypertension 1989;13(suppl):I80–93.

54. Berl T, Hunsicker LG, Lewis JB, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. J Am Soc Nephrol 2005;16:2170–9.

55. Hansson L, Zanchetti A, Carruthers SG, *et al.* Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet 1998; 351:1755–62.

56. Yildiz A, Memisoglu E, Oflaz H, et al. Atherosclerosis and vascular calcification are independent predictors of left ventricular hypertrophy in chronic haemodialysis patients. Nephrol Dial Transplant 2005;20:760–7.

57. Pinto–Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. Ann Intern Med 2000;133:585–91.

58. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995;47:186–92.

59. Zoccali C, Benedetto FA, Mallamaci F, *et al.* Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. J Am Soc Nephrol 2001;12:2768–74.

60. Grassi G, Seravalle G, Calhoun DA, et al. Mechanisms responsible for sympathetic activation by cigarette smoking in humans. Circulation 1994;90:248–53.

61. Ritz E, Benck U, Franek E, Keller C, Seyfarth M, Clorius J. Effects of smoking on renal hemodynamics in healthy volunteers and in patients with glomerular disease. J Am Soc Nephrol 1998;9:1798–804.

62. Pinto–Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. Ann Intern Med 2000;133:585–91.

63. Orth SR, Hallan SI. Smoking: a risk factor for progression of chronic kidney disease and for cardiovascular morbidity and mortality in renal patients—absence of evidence or evidence of absence? Clin J Am Soc Nephrol 2008;3:226–36.

64. Kamimura MA, Carrero JJ, Canziani ME, Watanabe R, Lemos MM, Cuppari L. Visceral obesity assessed by computed tomography predicts cardiovascular events in chronic kidney disease patients. Nutr Metab Cardiovasc Dis 2013;23:891–7.

65. de Mutsert R, Snijder MB, van der Sman–de Beer F, et al. Association between body mass index and mortality is similar in the hemodialysis population and the general population at high age and equal duration of follow-up. J Am Soc Nephrol 2007;18:967–74.

66. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421–6.

67. Lee KU, Park JY, Kim SW, et al. Prevalence and associated features of albuminuria in Koreans with NIDDM. Diabetes Care 1995;18:793–9.

68. Mykkanen L, Zaccaro DJ, O'Leary DH, Howard G, Robbins DC, Haffner SM. Microalbuminuria and carotid artery intima-media thickness in nondiabetic and NIDDM subjects. The Insulin Resistance Atherosclerosis Study (IRAS). Stroke 1997;28:1710–16.

69. Suzuki K, Kato K, Hanyu O, Nakagawa O, Aizawa Y. Left ventricular mass index increases in proportion to the progression of diabetic nephropathy in type 2 diabetic patients. Diabetes Res Clin Pract 2001;54:173–80.

70. Wachtell K, Ibsen H, Olsen MH, et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE study. Ann Intern Med 2003;139:901–6.

71. Stehouwer CD, Nauta JJ, Zeldenrust GC, Hackeng WH, Donker AJ, den Ottolander GJ. Urinary albumin excretion, cardiovascular disease, and endothelial dysfunction in non-insulin-dependent diabetes mellitus. Lancet 1992;340:319–23.

72. Stehouwer CD, Lambert J, Donker AJ, van Hinsbergh VW. Endothelial dysfunction and pathogenesis of diabetic angiopathy. Cardiovasc Res 1997;34:55–68.

73. Festa A, D'Agostino R, Howard G, Mykkanen L, Tracy RP, Haffner SM. inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: the Insulin Resistance Atherosclerosis Study. Kidney Int 2000;58:1703–10.

74. Silberberg J, Racine N, Barre P, Sniderman AD. Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. Can J Cardiol 1990;6:1–4.

75. Weiner DE, Tighiouart H, Vlagopoulos PT, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. J Am Soc Nephrol 2005;16:1803–10.

76. Besarab A, Bolton WK, Browne JK, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 1998;339:584–90.

77. Weiner DE, Tighiouart H, Vlagopoulos PT, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. J Am Soc Nephrol 2005;16:1803–10.

78. G.A. Block, P.S. Klassen, J.M. Lazarus, N. Ofsthun, E.G. Lowrie, G.M. Chertow, Mineral metabolism, mortality, and morbidity in maintenance hemodialysis, J. Am. Soc.Nephrol. 15 (2004) 2208–2218.

79. M. Tonelli, F. Sacks, M. Pfeffer, Z. Gao, G. Curhan, Relation between serum phosphate level and cardiovascular event rate in people with coronary disease, Circulation 112 (2005) 2627–2633.

80. M. Chonchol, R. Dale, R.W. Schrier, R. Estacio, Serum phosphorus and cardiovascular mortality in type 2 diabetes, Am. J. Med. 122 (2009) 380–386.

81. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004;15:2208–18.

82. Pannier B, Guérin AP, Marchais SJ, Safar ME, London GM. Stiffness of capacitive and conduit arteries: prognostic significance for end-stage renal disease patients. Hypertension 2005; 45: 592-596

83. Jovanovich A, Ix JH, Gottdiener J, McFann K, Katz R, Kestenbaum B, de Boer IH, Sarnak M, Shlipak MG, Mukamal KJ, Siscovick D, Chonchol M. Fibroblast growth factor 23, left ventricular mass, and left ventricular hypertrophy in community-dwelling older adults. Atherosclerosis 2013; 231: 114-119

84. Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. JAMA 2007;298:1163-70

85. Negri AL. Fibroblast growth factor 23: associations with cardiovascular disease and mortality in chronic kidney disease. Int Urol Nephrol 2014;46:9–17.

86. Scialla, J.J. & M. Wolf. Nat. Rev. Nephrol. 10, 268–278 (2014).

87. Kato S, Chmielewski M, Honda H, et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol 2008;3:1526–33.

88. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. Circulation 2003;107:87–92.

89. Opatrny K Jr. Clinical importance of biocompatibility and its effect on haemodialysis treatment. Nephrol Dial Transplant 2003;18(suppl 5):v41–4.

90. Opatrny K Jr. Clinical importance of biocompatibilityand its effect on haemodialysis treatment. Nephrol Dial Transplant 2003;18(suppl 5):v41–4.

91. Ross R. Atherosclerosis--an inflammatory disease. N EnglJ Med 1999; 340: 115-126 [PMID: 9887164 DOI: 10.1056/NEJM199901143400207]

92. Menon V, Greene T, Wang X, et al. C-Reactive protein and albumin as predictors of all-cause and cardiovascular mortality in chronic kidney disease. Kidney Int 2005;68:766–72.

93. Naruko T, Ueda M, Haze K, et al. Neutrophil infiltration of culprit lesions in acute coronary syndromes. Circulation 2002;106:2894–900.

94. Hasegawa M, Ishii J, Kitagawa F, et al. Urinary neutrophil gelatinase-associated lipocalin as a predictor of cardiovascular events in patients with chronic kidney disease. Heart Vessels 2013;:[Epub ahead of print].

95. Yilmaz MI, Sonmez A, Saglam M, Qureshi AR, Carrero JJ, Caglar K, Eyileten T, Cakir E, Oguz Y, Vural A, Yenicesu M, Lindholm B, Stenvinkel P, Axelsson J. ADMA levels correlate with proteinuria, secondary amyloidosis, and endothelial dysfunction. J Am Soc Nephrol 2008; 19: 388-395

96. Kalanthar-Zadeh K, Balakrishnan VS. The kidney disease wasting: inflammation, oxidative stress, and diet–gene interaction. Hemodyalisis Int. 2006;10:315–325. doi: 10.1111/j.1542-4758.2006.00124.x.

97. Kalanthar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition–inflammation complex syndrome in dialysis patients: causes and consequences. Am J Kidney Dis. 2003;42:864–881. doi: 10.1016/j.ajkd.2003.07.016.

98. Delafontaine P, Yoshida T. The Renin-Angiotensin System And The Biology Of Skeletal Muscle: Mechanisms Of Muscle Wasting In Chronic Disease States. *Trans Am Clin Climatol Assoc*. 2016;127:245-258

99. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003;108:2154–69.

100. Elsayed EF, Tighiouart H, Griffith J, et al. Cardiovascular disease and subsequent kidney disease. Arch Intern Med 2007;167:1130–6.

101. London GM, Parfrey PS. Cardiac disease in chronic uremia: pathogenesis. Adv Ren Replace Ther 1997;4:194–211.

102. Mark PB, Johnston N, Groenning BA, *et al.* Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. Kidney Int 2006;69:1839–45

103. Nardi, E., Palermo, A., Mulè, G., et al. (2009). Left ventricular hypertrophy and geometry in hypertensive patients with chronic kidney disease.J Hypertens, 27(3), 633–41.

104. Foley, R. N., Parfrey, P. S., Kent, G. M., et al. (1998). Long-term evolution of cardiomyopathy in dialysis patients. Kidney Int, 54(5), 1720

105. Selvetella, G., Hirsch, E., Notte, A., et al. (2004). Adaptive and maladaptive hypertrophic pathways: points of convergence and divergence. Cardiovasc Res, 63(3), 373–80.

107. Ganau, A., Devereux, R. B., Roman, M. J., et al. (1992). Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. J Am Coll Cardiol, 19(7), 1550–8.

108. Shimizu, G., Hirota, Y., Kita, Y., *et al.* (1991). Left ventricular mid wall mechanics in systemic arterial hypertension. Myocardial function is depressed in pressure-overload hypertrophy. *Circulation*, 83(5), 1676–84.

109. Ozkahya, M., Ok, E., Cirit, M., *et al.* (1998). Regression of left ventricular hypertrophy in haemodialysis patients by ultrafiltration and reduced salt intake without antihypertensive drugs. *Nephrol Dial Transplant*, 13(6), 1489–93.

110. Du, Y., Plante, E., Janicki, J. S., *et al.* (2010). Temporal evaluation of cardiac myocyte hypertrophy and hyperplasia in male rats secondary to chronic volume overload. *Am J Pathol*, 177(3), 1155–63.

111. Stewart GA, Foster J, Cowan M, et al. Echocardiography overestimates left ventricular mass in hemodialysis patients relative to magnetic resonance imaging. *Kidney Int.* 1999;56:2248-2253.

112. Zoccali C, Benedetto FA, Mallamaci F, et al. Prognostic impact of the indexation of left ventricular mass in patients undergoing dialysis. *J Am Soc Nephrol.* 2001;12:2768-2774

113. Ritz E. Left ventricular hypertrophy in renal disease: beyond preload and afterload. *Kidney Int.* 2009;75:771-773.

114. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. *Clin J Am Soc Nephrol.* 2009;4:914-920.

115. Zoccali C, Benedetto FA, Mallamaci F, et al. Left ventricular mass monitoring in the follow up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int.* 2004;65:1492-1498.

116. London GM, Pannier B, Guerin AP, et al. Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. J Am Soc Nephrol. 2001;12:2759-2767.

117. Ritz E. Left ventricular hypertrophy in renal disease: beyond preload and afterload. Kidney Int. 2009;75:771-773

118. Y. Havlucu, S. Kursat, C. Ekmekci, P. Celik, S. Serter, O. Bayturan, et al, Pulmonary hypertension in patients with chronic renal failure, Respiration 74 (2007) 503–510.

119. Agarwal R. Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. Nephrol Dial Transplant 2012; 27(10): 3908–3914
120. M. Yigla, Z. Abassi, S.A. Reisner, F. Nakhoul, Pulmonary hypertension in hemodialysis patients: an unrecognized threat, Semin. Dial. 19 (5) (2006) 353–357.

121. Selvaraj S, Shah SJ, Ommerborn MJ, et al. Pulmonary hypertension is associated with a higher risk of heart failure hospitalization and mortality in patients with chronic kidney disease: The Jackson Heart Study. Circ Heart Fail 2017; 10(6): e003940.

122. Kawar B, Ellam T, Jackson C, et al. Pulmonary hypertension in renal disease: epidemiology, potential mechanisms and implications. Am J Nephrol 2013; 37(3): 281–290.

123. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. Intensive Care Med. 2008;34:957–962. doi: 10.1007/s00134-008-1017-8

124. C. Ronco , The cardiorenal syndrome: basis and common ground for a multidisciplinary patient-oriented therapy Cardiorenal Med, 1 (2011), pp. 3-4

125. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J: High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 2007;13:422–430

126. Hebert K, Dias A, Delgado MC, Franco E, Tamariz L, Steen D, Trahan P, Major B, Arcement LM: Epidemiology and survival of the five stages of chronic kidney disease in a systolic heart failure population. Eur J Heart Fail 2010;12:861–865.

127. Acute Dialysis Quality Initiative (ADQI). www.ADQI.org (accessed January 10, 2013).

128. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B: The severe cardiorenal syndrome: 'Guyton revisited'. Eur Heart J 2005;26:11–17

129. J. Redóna, L. Cea-Calvob, J.V. Lozanoc,*et al.*Kidney function and cardiovascular disease in the hypertensive population: the ERIC-HTA study J Hypertens, 24 (2006), pp. 663-669

130. A. Levin, J. Singer, C.R. Thompson, H.Ross, M. Lewis Prevalent left ventricular hypertrophy in the predialysis population: identifying opportunities for intervention Am J Kidney Dis, 27 (3) (1996), pp. 347-354

131. McCollough PA. Why is chronic kidney disease the 'spoiler' for cardiovascular outcomes? J Am Coll Cardiol. 2003;41:725–728. doi: 10.1016/S0735-1097(02)02955-8

132. Kottgen A, Russell SD, Loehr LR, et al. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. J Am Soc Nephrol. 2007;18:1307–1315. doi: 10.1681/ASN.2006101159.

133. Cai Q, Mukku VK, Ahmad M. Coronary artery disease in patients with chronic kidney disease: a clinical update. Curr Cardiol Rev 2013;9:331–9.

134. Sharma R, Pellerin D, Gaze DC, et al. Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates. Nephrol Dial Transplant 2005;20:2207–14.

135. Rabbat CG, Treleaven DJ, Russell JD, et al. Prognostic value of myocardial perfusion studies in patients with end-stage renal disease assessed for kidney or kidney-pancreas transplantation: a meta-analysis. J Am Soc Nephrol 2003;14:431–9.

136. Subbiah AK, et al. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup. Heart Asia 2016;8:56–61.

137. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. J Am Coll Cardiol 2003;42:201–8.

138. Palmer SC, Di Micco L, Razavian M, et al. Antiplatelet agents for chronic kidney disease. Cochrane Database Syst Rev 2013;(2):CD008834.

139. Efrati S, Zaidenstein R, Dishy V, et al. ACE inhibitors and survival of hemodialysis patients. Am J Kidney Dis 2002;40:1023–9.

141. Takahashi A, Takase H, Toriyama T, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis -a randomized study. Nephrol Dial Transplant 2006;21:2507–12.

142. Badve SV, Roberts MA, Hawley CM, et al. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:1152–61.

143. Manske CL, Wang Y, Rector T, et al. Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. Lancet 1992;340:998–1002.

144. Dragu R, Behar S, Sandach A, et al. Should primary percutaneous coronary intervention be the preferred method of reperfusion therapy for patients with renal failure and ST-elevation acute myocardial infarction? Am J Cardiol 2006;97:1142

145. Hobbach HP, Gibson CM, Giugliano RP, et al. The prognostic value of serum creatinine on admission in fibrinolytic-eligible patients with acute myocardial infarction. J Thromb Thrombolysis 2003;16:167–74.

146. Parikh, N. I. *et al.* Cardiovascular Disease Risk Factors in Chronic Kidney Disease. *Arch. Intern. Med.* **166,** 1884 (2006).

147. Rajapurkar, M. M. *et al.* What do we know about chronic kidney disease in India: first report of the Indian CKD registry. *BMC Nephrol.* **13,** 10 (2012).

148. Adler, A., Stratton, I. & Neil, H. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *Bmj* **321,** 412–419 (2000).

149. Lv, J. *et al.* Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: a systematic review and meta-analysis. *PLoS Med.* **9,** e1001293 (2012).

150. Kalantar-Zadeh, K., Abbott, K. C., Salahudeen, A. K., Kilpatrick, R. D. & Horwich, T. B. Survival advantages of obesity in dialysis patients. *Am. J. Clin. Nutr.* **81,** 543–554 (2005).

151. Nakamura, K. *et al.* Smoking increases the risk of all-cause and cardiovascular mortality in patients with chronic kidney disease. *Kidney Int.* **88,** 1144–1152 (2015).

152. Cheungpasitporn, W. *et al.* High alcohol consumption and the risk of renal damage: a systematic review and meta-analysis. *QJM An Int. J. Med.* **108,** 539–548 (2015).

153. McQuarrie, E. P. *et al.* Association between proteinuria and left ventricular mass index: a cardiac MRI study in patients with chronic kidney disease. *Nephrol. Dial. Transplant.* **26,** 933–938 (2011).

154. Abraham, G. *et al.* C-Reactive protein, a valuable predictive marker in chronic kidney disease. *Saudi J. Kidney Dis. Transpl.* **20,** 811–5 (2009).

155. Laddha, M., Sachdeva, V., Diggikar, P. M., Satpathy, P. K. & Kakrani, A. L. Echocardiographic assessment of cardiac dysfunction in patients of end stage renal disease on haemodialysis. *J. Assoc. Physicians India* **62,** 28–32 (2014).

156. Ahmed, A. *et al.* Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am. J. Cardiol.* **99,** 393–8 (2007).

157. House, A. A. Management of Heart Failure in Advancing CKD: Core Curriculum 2018. *Am. J. Kidney Dis.* **72,** 284–295 (2018).

158. Covic, A., Siriopol, D. & Voroneanu, L. Dialysis-induced segmental wall motion abnormalities, post-dialysis fatigue and cardiovascular mortality: the new Bermuda triangle? *Nephrol Dial Transpl.* **28,** 2404–2406 (2013).

159. Navaneethan, S. D. *et al.* Prevalence, Predictors, and Outcomes of Pulmonary

Hypertension in CKD. *J. Am. Soc. Nephrol.* **27,** 877–86 (2016).

160. Levin, A. *ANEMIA IN PREDIALYSIS AND DIALYSIS PATIENTS Anemia and left ventricular hypertrophy in chronic kidney disease populations: A review of the current state of knowledge*. *Kidney International* **61,** (2002).

161. Chang, J.-M., Chen, S.-C., Huang, J.-C., Su, H.-M. & Chen, H.-C. Anemia and Left Ventricular Hypertrophy With Renal Function Decline and Cardiovascular Events in Chronic Kidney Disease. *Am. J. Med. Sci.* **347,** 183–189 (2014).

162. Sonkar, S. K. *et al.* Vitamin D levels and other biochemical parameters of mineral bone disorders and their association with diastolic dysfunction and left ventricular mass in young nondiabetic adult patients with chronic kidney disease. *Saudi J. Kidney Dis. Transpl.* **28,** 758–763

163. Ghosh, B. *et al.* The high prevalence of chronic kidney disease-mineral bone disorders: A hospital-based cross-sectional study. *Indian J. Nephrol.* **22,** 285–91 (2012).

164. Uribarri, J. Phosphorus Homeostasis in Normal Health and in Chronic Kidney Disease Patients with Special Emphasis on Dietary Phosphorus Intake. doi:10.1111/j.1525-139X.2007.00309.

165. Brandenburg, V. M. *et al.* From skeletal to cardiovascular disease in 12 steps — the evolution of sclerostin as a major player in CKD-MBD Canonical Wnt pathway Sclerosn : mode of acϴon. 195–206 (2016). doi:10.1007/s00467-015-3069-7

166. Rivara, M. B. *et al.* Uncorrected and Albumin-Corrected Calcium, Phosphorus, and Mortality in Patients Undergoing Maintenance Dialysis. *J. Am. Soc. Nephrol.* 1–11 (2015). doi:10.1681/ASN.2014050472

167. Dobre, M. *et al.* Association of Serum Bicarbonate With Risk of Renal and Cardiovascular Outcomes in CKD: A Report From the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am. J. Kidney Dis.* **62,** 670–678 (2013).

168. Major, R. W. *et al.* Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis. *PLoS One* **13,** e0192895 (2018).

ANNEXURES

ANNEXURES

PROFORMA FOR DATA COLLECTION

TITLE : SUBCLINICAL CARDIAC ABNORMALITIES IN VARIOUS STAGES OF CKD

NAME: IP NO:

AGE:

SEX:

ADDRESS:

OCCUPATION:

DETAILED HISTORY:

GENERAL PHYSICAL EXAMINATION:

PULSE:

BLOOD PRESSURE:

JVP :

PALLOR:

PEDAL EDEMA :

SYSTEMIC EXAMINATION:

CARDIOVASCULAR EXAMINATION:

RESPIRATORY EXAMINATION:

PER ABDOMINAL EXAMINATION:

CENTRAL NERVOUS SYSTEM EXAMINATION:

LABORATORY DATA:

- HbA1c
- Fasting lipid profile.
- Renal function tests
- Complete blood count
- Urine analysis
- Serum Calcium
- Serum Phosphorous
- CRP

1. ECG
2. ULTRASOUND ABDOMEN : Kidney Size and echotexture :
3. ECHOCARDIOGRAM
    i. Interventricular Septum Thickness :
    ii. Ejection Fraction :
    iii. Systolic Dysfunction :
    iv. Diastolic Dysfunction (e/A Ratio) :

INFORMED CONSENT FORM

STUDY TITLE: SUBCLINICAL CARDIAC ABNORMALITIES IN VARIOUS STAGES OF CKD

STUDY NUMBER:

SUBJECT'S NAME: **HOSPITAL NUMBER:**

AGE:

Detecting cardiac abnormalities before they clinically manifest as breathlessness and heart attack in early stages of CKD will help us understand the disease better and will throw light on ways to prevent such occurrence. It is hoped that the knowledge of subclinical cardiac abnormalities in CKD might be useful for early identification of patients at high risk of cardiovascular morbidity and hence help us in managing such patients better .

We will be subjecting you to routine blood investigations , USG Abdomen and 2D ECHO as part of this study .

If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. This information collected will be used for only dissertation and publication. The institutional ethical committee has reviewed this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understood the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I,the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation and publication only.

Signature or thumb impression of the subject: Date:

Name and signature of the witness: Date:

KEY TO MASTER CHART

SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
ESR	Erythrocyte Sedimentation Rate
EF	Ejection Fraction
RBS	Random Blood Sugar
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
VLDL	Very Low Density Lipoprotein
eGFR	estimated Glomerular Filtration Rate
CRP	C-Reactive Protein
IVSd	Interventricular Septal thickness Diastolic
IVSs	Interventricular Septal thickness Systolic
LVs	Left Ventricular Systolic thickness
LVd	Left Ventricular Diastolic thickness
LA dia	Left Atrial Diameter
PASP	Pulmonary Artery Systolic Pressure
RV dia	Right Ventricular diameter

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT
1	HOSP NO.	AGE	SEX	HEIGHT (cm)	WEIGHT	BMI	PULSE	SBP	DBP	DIABETES	HYPERTENSION	SMOKING	ALCOHOLISM	HEMOGLOBIN	TOTAL COUNTS	ESR	RBS	S.CHOLESTEROL	HDL	LDL	VLDL (2-30)	S.Creatinine	eGFR	CRP	S.ALBUMIN	SODIUM	POTASSIUM	BICARBONATE	CALCIUM	PHOSPHOROUS (2.5-4.5)	HBA1C	URINE ALBUMIN	IVSd(mm)	IVSs(mm) 12.2 ± 1.71	LV Mass (g)	LV Mass Index (g/m2)	LV Hypertrophy	LV diameter (Systolic)	LV diameter diastolic (mm)	LA diameter	PWd	RV diameter	Diastolic Dysfunction	EF %	RWMA	PASP
2	371592	58	FEMALE	166	62	22.5	110	180	90	YES	YES	NO	NO	8	11340	30	184	220	20	50	20	6.5	6.5	HIGH	3.6	136	5.2	24	7.8	6.4	7	3+	16	18	283	163	Present	29.8	45.5	40	14	29	Present	60%	nil	32
3	461116	56	MALE	168	64	22.6	88	150	90	YES	YES	YES	NO	7.8	9800	45	197	210	36	96	22	8.3	6.5	HIGH	2.8	132	5.6	24	7.2	7.2	7.5	3+	16	18	299	173	Present	27	46	41	15	30	Present	60%	nil	20
4	452477	58	FEMALE	156	66	27.1	84	160	94	YES	YES	NO	NO	8.9	13200	45	170	200	28	120	35	6.6	6.4	LOW	2.9	128	5.4	20	7.8	5.4	8.4	2+	15	17.5	264	156	Present	26	44	40	15	30	Present	60%	nil	28
5	478882	52	MALE	158	64	25.3	112	160	94	YES	YES	YES	NO	11	14300	45	120	198	32	124	40	7.9	7.2	LOW	3.8	135	5.5	18	8.4	4.8	8.8	1+	15	17.5	251	150	Present	25	44	39	14	28	Present	30%	nil	30
6	467412	64	MALE	164	58	21.5	72	140	84	YES	YES	YES	NO	10	8400	40	159	180	35	100	25	7.9	6.5	LOW	3.2	132	5.4	19	8.8	6.4	7.6	1+	16	17.2	262	153	Present	29	45	40	14	31	Present	60%	nil	22
7	530846	66	MALE	168	68	24	76	150	72	YES	YES	YES	NO	13	8600	64	164	198	38	98	22	6.8	7.7	LOW	2.8	134	5.2	18	8.4	7.2	7.2	3+	16	17.5	282	158	Present	32	46	42	14	31	Present	60%	nil	20
8	559444	56	MALE	164	66	23.9	72	144	76	YES	YES	NO	NO	10	9600	40	166	196	30	110	36	4.8	13	HIGH	2.5	133	5.2	22	7.8	7.4	7.7	3+	16	17	284	164	Present	30	47	43	13	30	Present	60%	nil	25
9	553981	58	MALE	162	56	21	112	168	84	YES	YES	NO	YES	7.6	8450	22	170	194	28	140	42	4.2	15	HIGH	2.9	132	5	19	7.5	6.8	9	1+	15	18	288	168	Present	28	44	43	16	29	Present	30%	nil	35
10	678882	65	MALE	164	54	20	110	156	80	YES	YES	YES	NO	7.8	5600	18	150	168	42	122	38	4.5	13	LOW	3	131	4.5	20	7.8	4	9.5	3+	15	17.2	256	158	Present	27	45	42	14	29	Present	60%	nil	28
11	530564	62	FEMALE	156	60	24	108	144	84	NO	YES	NO	NO	12	7200	10	158	172	32	135	32	6.7	6.1	LOW	2.6	130	5.2	22	8.4	3.8	5.6	2+	16	17.4	262	162	Present	28	45	44	14	28	Present	45%	nil	30
12	560240	67	FEMALE	154	54	22	120	138	88	NO	YES	NO	NO	11	5680	10	142	190	30	122	35	5.4	7.6	LOW	2.5	135	5.4	23	8.5	6.8	5.8	2+	14	17.5	250	159	Present	28	45.5	42	14	29	Present	60%	nil	25
13	555514	58	MALE	155	68	28	96	166	82	YES	YES	YES	NO	10	6480	18	172	196	36	98	15	6.6	8.4	HIGH	3.2	134	5.2	21	7.8	5.8	7.5	3+	16	17.2	275	165	Present	34	45.6	42	14	30	Present	45%	nil	32
14	556265	52	MALE	158	68	28	88	164	76	YES	YES	NO	YES	9.4	7250	15	178	196	38	96	20	6.6	8.8	HIGH	3.5	137	5.4	20	7.2	6.4	8.6	1+	15	17	272	157	Present	29	45.2	42	15	31	Present	60%	nil	20
15	556265	48	FEMALE	164	58	21.5	88	156	90	NO	YES	NO	NO	10	5600	22	190	198	28	84	22	6.1	7.5	HIGH	2.4	138	5.2	20	7.8	5.5	5.6	1+	15	18	266	167	Present	28	45.8	40	14	29	Present	30%	nil	35
16	461234	46	MALE	158	64	25.6	84	152	90	NO	YES	YES	NO	12	6450	14	220	200	32	88	15	8.5	6.8	HIGH	2.5	128	3.8	18	8.4	4.2	4.8	1+	16	17.2	276	165	Present	32	45.5	42	15	28	Present	60%	nil	25
17	74928	56	MALE	170	68	23	88	168	94	NO	YES	NO	NO	11	8600	24	250	184	30	72	18	3.5	18	LOW	3	128	4.5	22	7.5	4.8	6.5	3+	16	17.5	280	164	Present	30	45.5	40	14	27	Present	60%	nil	24
18	27218	55	FEMALE	158	72	28	88	160	96	NO	YES	NO	NO	10	7450	25	270	182	30	80	10	2.5	20	LOW	3.5	130	4.8	25	7.8	4.8	6.4	3+	15	17.5	286	168	Present	29.2	45.8	42	15	27	Present	42%	present	25
19	174268	60	FEMALE	160	66	25	100	150	90	NO	YES	NO	NO	9.8	2800	26	158	194	45	84	18	2.1	25	LOW	2.8	131	5.2	26	8.4	4.4	6.2	1+	16	18	250	146	Present	31	42	38	15	27	Present	50%	nil	32
20	604161	56	MALE	170	66	22	84	154	84	YES	YES	NO	NO	13	6500	28	190	172	32	86	20	2.8	24	HIGH	2.7	132	5.5	27	7.8	4.6	8.4	2+	16	18	269	152	Present	27	43	38	15	27	Present	40%	nil	27
21	77450	58	MALE	174	68	22	88	152	88	YES	YES	NO	YES	11	8640	22	132	178	28	78	25	2.7	25	HIGH	2.5	135	5.4	25	7.5	4.8	8.6	2+	16	18	252	139	Present	26.4	42	38	14	27	Present	45%	nil	25
22	282791	55	MALE	172	65	21.9	84	164	100	YES	YES	YES	YES	13	4750	10	147	186	22	74	25	3	22	LOW	3	136	5.5	22	6.8	4.6	7.2	1+	15	17.5	215	122	Present	26.8	40	38	14	27	Present	60%	nil	28
23	304427	64	MALE	164	67	24	76	166	88	NO	YES	YES	NO	13	5600	8	154	184	25	120	38	3.1	20	LOW	3.2	137	5.8	18	6.8	5.4	5.6	3+	15	18	229	131	Present	27.2	41	38	14	27	Present	60%	nil	22
24	81154	65	FEMALE	162	66	21	80	170	84	NO	YES	YES	NO	13	6200	20	215	164	24	122	35	2.9	16	LOW	2.5	130	5.2	23	7.4	4	5.8	3+	14	17.5	215	119	Present	27.8	42	36	13	27	Present	50%	nil	18
25	280198	66	MALE	168	56	19	84	172	86	NO	YES	NO	NO	11	7500	22	312	184	28	142	42	3.3	19	LOW	2.5	135	5.8	20	7.5	3.8	4.8	1+	14	15	215	114	Present	27.5	42	38	13	28	Present	45%	nil	14
26	49655	68	FEMALE	178	60	18	88	170	100	NO	YES	NO	NO	12	8600	25	335	188	32	85	22	2.5	19	LOW	3	134	5.5	23	7.5	3.5	5.6	3+	15	16	229	128	Present	26.5	41.8	38	14	28	Absent	45%	nil	16
27	75220	62	MALE	172	66	22.3	84	156	80	NO	YES	NO	NO	11	7250	24	148	184	33	88	28	3.1	21	HIGH	2.4	136	4.5	22	7.4	4.2	5.8	2+	15	16.2	243	137	Present	27.4	42.7	38	14	27	Absent	45%	present	25
28	287028	60	FEMALE	172	66	22.3	84	154	88	NO	YES	YES	NO	11	8700	22	172	190	30	86	22	2.3	22	HIGH	3.5	132	4.2	19	7.8	4.56	5.8	2+	14	15.5	218	123	Present	27.5	41.5	36	13	27	Absent	50%	nil	25
29	302955	66	MALE	168	68	24	84	158	84	NO	YES	YES	NO	11	7500	26	174	184	28	80	28	2.8	23	HIGH	3	133	4.2	22	7.4	4.8	5.4	1+	15	15.5	209	117	Present	27	40	36	13	27	Absent	50%	nil	24
30	287045	60	MALE	164	64	23	88	154	90	YES	YES	YES	NO	12	12560	28	158	188	28	98	25	2.4	28	HIGH	2.8	135	4.5	22	8.4	4.4	8.5	3+	15	15	207	121	Present	27.4	38	36	14	27	Present	60%	present	28
31	288246	56	FEMALE	164	68	24.1	110	134	96	YES	YES	YES	YES	11	13250	22	172	186	26	94	26	2.1	25	LOW	2.4	136	4.8	24	9.2	4.5	9.2	2+	15	16	237	135	Present	25.4	42	37	14	28	Present	50%	nil	24
32	280198	55	FEMALE	166	56	20.7	100	148	100	YES	YES	NO	YES	12	11000	18	178	190	34	96	32	2.3	23	LOW	2.8	132	4.8	23	9.8	3.5	8	1+	14	15	201	107	Present	26.8	40.5	37	13	28	Absent	50%	nil	22
33	260765	58	MALE	168	64	22	84	144	100	NO	YES	NO	NO	12	12678	15	194	172	38	88	24	2	35	LOW	2.8	133	4.5	23	9.2	3.6	5.4	2+	14	15	238	126	Present	27.2	39	36	13	28	Present	50%	nil	22
34	243388	60	MALE	162	56	21.3	88	156	90	NO	NO	NO	NO	12	8430	10	152	156	32	78	28	1.9	36	LOW	3	134	4.8	25	7.8	3.8	4.9	1+	13	15	175	93	Present	27.8	40.2	36	12	28	Absent	45%	present	22
35	272332	55	MALE	168	58	21.5	100	164	84	NO	NO	NO	NO	11	5600	15	148	154	42	100	40	1.7	46	LOW	4.2	135	4.2	23	7.8	2.8	5	1+	14	15	201	107	Present	25.8	40.1	36	13	27	Absent	45%	nil	20
36	284090	54	MALE	168	56	19.8	110	168	84	YES	YES	NO	NO	8.4	5870	14	150	158	32	120	32	1.7	45	LOW	4.5	138	4.2	22	8.8	3	7.5	2+	14	15	175	94	Present	26.4	39	36	12	27	Present	50%	nil	25
37	78399	56	MALE	174	64	21.1	120	154	88	YES	YES	NO	YES	11	6500	18	164	172	32	110	34	1.5	51	HIGH	4.4	132	4.5	23	9.4	3	7.8	1+	14	15	178	94	Present	26.5	39.5	36	12	27	Present	50%	nil	25
38	300868	55	FEMALE	176	68	21	110	152	90	YES	NO	YES	NO	11	6450	10	168	184	36	98	22	1.5	38	HIGH	3.5	134	4.8	24	9.8	3	6.5	1+	13	15	177	97	Present	27.2	40.2	36	12	28	Absent	50%	nil	21
39	283545	54	MALE	177	66	21.1	98	156	94	YES	NO	YES	YES	12	7200	10	172	188	36	84	25	1.8	41	LOW	3.6	135	4.8	23	9.5	3.6	6.5	1+	13	14	159	86	Present	25.8	39.8	37	11	28	Absent	60%	nil	22
40	166738	48	MALE	168	58	20.5	100	164	100	NO	YES	YES	YES	11	8650	10	178	210	32	82	28	1.5	53	LOW	2.5	136	4.5	22	9.5	3.8	6.3	1+	13	14	176	97	Present	25.5	42	36	11	29	Absent	60%	nil	15
41	289043	50	FEMALE	168	64	22	120	160	84	NO	YES	NO	NO	9.8	4500	8	215	200	34	80	22	1.1	57	LOW	2.5	132	4.5	26	9.4	3.84	6.4	1+	13	14	167	93	Present	27.2	41	37	11	28	Absent	60%	nil	15
42	283306	50	FEMALE	178	74	23.5	110	170	80	NO	YES	NO	NO	11	5500	10	224	198	32	86	25	1.4	43	LOW	2.8	132	3.8	24	9.5	2.8	6.5	1+	13	14	187	105	Present	26.4	40.5	38	13	28	Present	60%	nil	15
43	288983	55	MALE	172	64	21.6	108	156	100	NO	YES	NO	YES	11	5580	8	312	210	36	78	26	1.6	45	LOW	2.5	135	3.8	22	9.8	2.8	6.2	2+	12	14	155	83	Present	26.2	40.2	37	11	28	Present	60%	nil	15
44	292554	54	MALE	178	64	20	115	120	84	NO	NO	NO	YES	11	6800	8	345	215	38	70	28	1.4	55	LOW	2.2	136	3.8	22	9.5	2.5	6.4	1+	8	10	155	83	Absent	26.4	38	38	7	28	Absent	60%	nil	22
45	289349	56	MALE	168	56	19	96	110	80	NO	YES	NO	NO	12	8700	8	212	200	32	84	22	1.4	55	HIGH	2.8	138	3.8	24	7.8	3.8	6.5	1+	9	12	101	61	Absent	26.2	39.5	36	8.2	28	Absent	60%	nil	25
46	289483	55	MALE	166	68	24	100	150	84	YES	YES	YES	NO	13	7800	8	112	188	30	98	20	1.4	56	HIGH	3	137	3.8	24	7.6	3.6	8.4	1+	10	14	111	63	Absent	25.8	38.7	35	9	28	Present	60%	nil	22
47	284037	55	FEMALE	165	64	23.5	110	164	72	YES	NO	YES	NO	12	8000	8	98	198	28	90	30	1.1	55	HIGH	2.8	142	4.5	22	9	3.7	8.8	1+	10	14	121	70	Absent	27.6	40.2	35	9	27	Absent	60%	nil	15
48	393574	55	MALE	168	56	19	120	150	76	YES	NO	YES	YES	13	8500	10	86	190	28	90	32	1.4	58	HIGH	2.5	142	4.6	23	10	4.2	7.4	1+	11	14	132	82	Present	28.4	42.5	35	9	27	Absent	60%	present	14
49	297505	56	MALE	164	58	20	112	148	80	YES	YES	NO	YES	10	8450	10	110	194	40	98	20	1	84	HIGH	2.8	138	4.8	25	8.5	4	6.8	1+	12	14	144	90	present	25.8	40.5	36	10	27	Present	60%	present	12
50	287877	54	MALE	166	64	23	130	130	90	YES	YES	NO	YES	11	6500	8	118	198	42	120	38	1	82	HIGH	2.4	138	5.2	23	8.5	4.1	6.5	1+	10	12	142	82	Absent	25.4	41.5	36	9.3	26	Present	60%	present	12
51	299971	54	MALE	168	64	22	132	144	92	YES	YES	YES	YES	10	6600	10	122	196	42	110	32	1.1	75	LOW	2.5	142	5.2	23	8.5	3.5	6.6	1+	9	11	90	52	Absent	25.2	38	37	7.5	27	Present	60%	nil	12
52	344260	65	MALE	166	66	23	120	164	80	YES	YES	NO	YES	9.8	7000	10	154	194	38	134	30	1	77	LOW	2.5	142	4.8	22	8.4	3.8	6.8	1+	9	12	110	63	Absent	25.6	42	36	8	26	Absent	60%	nil	14
53	244378	61	FEMALE	168	68	24	110	170	80	YES	NO	NO	NO	11	7500	8	168	178	38	120	32	0.9	65	LOW	3.8	135	4.7	23	8.4	4	6.5	2+	10	12	130	73	Absent	25.8	42	37	9.2	27	Absent	60%	nil	14
54	162066	60	FEMALE	172	64	21	112	172	84	NO	NO	NO	NO	11	6250	8	172	150	42	100	32	0.9	67	LOW	3.6	136	4.5	23	8.4	3.5	6.6	1+	10	12	122	70	Absent	25.2	40	38	9.4	27	Absent	60%	nil	12
55	244378	64	FEMALE	170	65	22	108	120	80	NO	NO	NO	NO	10	5010	8	154	144	40	110	35	0.8	73	LOW	3.7	138	4.8	23	8.8	3.4	6.4	2+	9	11	114	65	Absent	24.8	42.1	36	9	26	Absent	60%	nil	12
56	185780	64	FEMALE	168	66	23	96	158	80	YES	YES	NO	NO	10	6500	8	172	132	30	110	32	0.8	75	LOW	3.8	135	4.5	23	9.8	3.4	6.8	1+	8	10	97	56	Absent	24.9	43.3	38	7.2	25	Present	60%	nil	14
57	301068	68	MALE	168	60	21	94	164	70	YES	YES	NO	NO	10	6700	8	168	134	32	84	20	1	73	LOW	3.5	140	4.8	23	9.5	3.2	7.2	1+	10	12	102	59	Absent	25.8	38.2	37	8	26	Present	60%	nil	13
58	252526	58	MALE	170	58	20	88	160	74	NO	NO	YES	NO	9.8	8600	10	190	137	34	88	22	1	78	LOW	3.8	142	4.4	25	10	2.5	6.3	1+	12	13	161	97	Present	25.5	41.8	37	10	26	Absent	50%	nil	12
59	648607	62	MALE	172	54	18	94	164	74	NO	NO	YES	NO	11	4500	8	200	138	36	86	25	1	81	LOW	3.5	142	4.2	23	11	2.6	6.2	2+	8	10	93	58	Absent	25.6	40.8	37	7.4	27	Absent	60%	nil	12
60	648754	64	MALE	178	55	17	96	162	78	YES	YES	NO	NO	11	5400	10	210	136	32	84	26	0.7	85	LOW	3.8	144	4.6	23	9.8	4.1	6.7	1+	9	11	112	68	Absent	25.7	42.6	36	8	25	Absent	50%	nil	12
61	648719	64	MALE	170	65	22	100	164	70	YES	YES	NO	NO	11	7500	10	222	134	34	82	27	0.7	89	LOW	3.6	142	4.5	23	9.9	3.5	8.4	3+	8	11	102	58	Absent	25.8	43.4	35	7.2	27	Absent	60%	nil	15

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT
62	643277	65	FEMALE	174	53	17	104	168	72	YES	YES	NO	NO	12	6500	8	254	132	36	120	32	0.8	77	LOW	3.8	138	4.6	22	8.4	2.8	7.6	1+	9	11	117	72	Absent	25.7	42.8	36	8.4	27	Absent	60%	nil	12
63	614581	52	FEMALE	176	64	19	102	120	80	YES	NO	NO	NO	13	8400	10	122	142	32	110	35	0.8	80	LOW	4.2	142	4.6	22	8.8	2.4	7.8	1+	10	12	125	71	Absent	25.6	42.4	35	8	25	Absent	60%	nil	12
64	637529	55	FEMALE	178	66	20.8	108	120	80	YES	NO	NO	NO	13	7500	8	128	144	34	80	20	0.8	77	LOW	3.8	138	4.5	24	8.4	2.8	7.6	1+	10	12	105	58	Absent	25.6	38	35	8.5	25	Absent	50%	nil	12
65	632752	58	MALE	172	54	18	94	164	74	NO	NO	YES	NO	11	4500	8	200	138	36	86	25	0.8	81	LOW	3.5	142	4.2	23	11	2.6	6.2	2+	8	10	93	58	Absent	25.6	40.8	37	7.4	27	Absent	60%	nil	12

	AU
1	E/A
2	0.8
3	1.3
4	1.2
5	1.4
6	0.9
7	1.2
8	1.2
9	1.3
10	1
11	1
12	1
13	0.8
14	0.8
15	0.9
16	0.9
17	0.8
18	0.8
19	0.8
20	0.7
21	0.6
22	0.7
23	0.7
24	0.7
25	0.7
26	0.7
27	0.7
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29	0.7
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31	0.7
32	0.6
33	0.8
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35	0.8
36	0.8
37	0.8
38	0.9
39	0.8
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55	0.8
56	0.9
57	0.9
58	0.9
59	0.9
60	0.9
61	0.8

	AU
62	0.8
63	1
64	0.9
65	0.9