Original Article

Cardiac Function Evaluation in Different Stages of Chronic Kidney Disease

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Background : In patients with Chronic Kidney Disease (CKD), cardiovascular physiological alteration occurs a lot and it becomes the most common cause of death in these patients.

Aims and Objective : to study the prevalence, correlation and association of Left Ventricular Diastolic Dysfunction (LVDD), Systolic Dysfunction (LVSD) and Left Ventricular Hypertrophy (LVH) with Left Ventricular Mass Index (LVMI) in relation to different stages of CKD patients.

Materials and Methods : it was a cross-sectional observational study involving 60 patients of established CKD patients after consideration of inclusion and exclusion criteria; tools used were estimated Glomerular Filtration Rate (eGFR) calculation for the staging of CKD and 2D echocardiography for grading and calculation of diastolic dysfunction, systolic dysfunction and LVMI. The data were analyzed by standard statistical methods.

Results : Most patients (41.6%) had grade II diastolic dysfunction seen mainly in stage IV patients and grade III dysfunction occurred in 66.7% of stage V patients. There was a significant association between systolic dysfunction and advanced stages of CKD. LVMI showed a progressive increase from stage I disease to stage V disease.

Conclusion : With advanced stages of CKD, there was a statistically significant increase in LVDD, LVMI and a statistical decrease in systolic function.

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Key words **: Chronic Kidney Disease, Left Ventricular Diastolic Dysfunction, Left Ventricular Systolic Dysfunction, Left Ventricular Mass Index, Estimated Glomerular Filtration Rate.**

Chronic Kidney Disease (CKD) is an important and common non-communicable condition globally. The prevalence of CKD among the Asian population is approximately 17%[1]. In patients with CKD, cardiovascular disease is the most common cause of death. Patients with eGFR below 60 ml/min/1.73m^2 are much more likely to die from Cardiovascular (CV) complications than to develop End Stage Renal Disease (ESRD).

Diminished estimated Glomerular Filtration Rate (eGFR) and albuminuria are powerful, graded, independent predictors of cardiovascular mortality, morbidity and all-cause mortality[2]. Patients with CKD have a high burden of conventional risk factors that lead to accelerated atherosclerosis, LV dilatation with hypertrophy, systolic dysfunction and high LV filling pressure along with numerous CVD risk factors specific to CKD.

One of the most common cardiac structural abnormalities in CKD patients is Left Ventricular Hypertrophy[2]. LV dysfunction particularly diastolic dysfunction initiates cardiovascular disease in CKD patients[3]. It is impaired LV relaxation and increased LV stiffness and can be associated with normal or abnormal systolic function. LV Systolic Dysfunction is most identified by a subnormal LV Ejection Fraction (LVEF). Furthermore, in hemodialysis patients and those with later stages of Chronic Kidney Disease, Coronary Artery Obstruction, reduced Coronary Reserve and LV functional and structural abnormality secondary to volume and pressure overload leads to the development of cardiomyopathy[4]. In later stages, left ventricular adaptation leads to decreased capillary density, LV dilatation, more severe diastolic dysfunction, conduction defects and eccentric hypertrophy. All of these predispose to sudden cardiac death in these patients[5].

Early detection of cardiac functional and structural abnormality with a proper intervention directed at the pathophysiological mechanism can delay the decline in cardiac function and decrease morbidity and

Editor's Comment :

- Chronic Kiney Diseases impose increased cardio-vascular morbidity and mortality. So, patients of Chronic Kidney Disease should be regularly screened for associated cardio-vascular disease. Prompt intervention can be taken up if cardio-vascular abnormality is detected early.

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mortality. Our purpose of the study was to determine the prevalence of LV Systolic and Diastolic Dysfunction in different stages of CKD and to evaluate the correlation and association of various echo-cardiography parameters (E/A, E/e', LA diameter, LVEF, fractional shortening, LVMI) of LV function with the stages.

Aims and Objectives

(1) To study the prevalence of Left Ventricular Diastolic Dysfunction, Left Ventricular Systolic Dysfunction and Left Ventricular Hypertrophy in different stages of Chronic Kidney Disease patients.

(2) To study the correlation and association of Diastolic Dysfunction and Systolic Dysfunction, Left Ventricular Mass Index with different stages of chronic kidney disease.

Materials and Methods

(A) Study Type : Cross-sectional observational study.

(B) Sample Size : 60 patients with CKD were enrolled.

(C) Sample Size Calculation : According to a study done by Shady Elhusseiny, *et al* in India showed that the correlation coefficient of E/E' with estimated GFR was 0.42[6]. Now considering 95% confidence interval and 95% precision; sample size was calculated using the equation[7] :

Total sample size =$N=[(Z\alpha + Z\beta)/C]^2 + 3$. Here, the standard normal deviate for $\alpha = Z\alpha = 1.9600$. The standard normal deviate for $\beta = Z\beta = 1.2816$. $C= 0.5 * \ln[(1+r)/(1-r)] = 0.4477$. So, total sample size = $N=[(1.96 + 1.2816)/0.4477]^2 + 3 = 55$. Minimum sample size needed = 55. We took 60 patients.

(D) Sampling Technique : Simple random sampling.

(E) Inclusion Criteria : All patients attending Medical College and Hospital OPD and admitted in the General Medicine Ward who are diagnosed as cases of Chronic Kidney Disease as per KDIGO guidelines.

(F) Exclusion criteria : Pre-existing cardiac disease like Rheumatic Heart Disease, Ischemic Heart Disease, Congenital Heart Disease, Myocarditis Due to Infective Etiology, Primary Heart Muscle Disease like Cardiomyopathies, patients with Acute Kidney Injury, pregnant or lactating women, patients who are unable to give informed consent

(G) Procedure : All CKD patients who have given consent for participation in this study have been evaluated with laboratory examinations and echocardiography. After filling of the proforma and consent, blood tests were done to detect renal function such as serum Urea and Creatinine and other co-morbidities like diabetes mellitus and anemia. During check-up, vitals were measured including blood pressure. Then echocardiography was done and parameters that were previously determined were noted. During the same time, other cardiovascular causes were ruled out.

We have used the Modification of Diet in Renal Disease (MDRD) Equation for calculating the estimated Glomerular Filtration Rate (eGFR) and classified them according to KDIGO guidelines 2012 which denotes G1>90 ml/min/1.73m^2, G2=60-90, G3=30-60, G4=15-30 and G5<15 ml/mi/1.73m^2.

We have used a 2D Echocardiography machine GE LOGIQ 400 PRO with a 3.5 MHz transducer probe. Two-dimensional echocardiography and M mode recording perpendicularly to the long axis of and through the center of the left ventricle at the papillary muscle level were taken as standard measurements of systolic and diastolic wall thickness and chamber dimensions. For measurement of left ventricular systolic function Left Ventricular Ejection Fraction (LVEF), regional wall motion abnormality and fractional shortening were taken. For measurement of left ventricular diastolic function E (early mitral inflow velocity), A (m/sec): late mitral inflow velocity, E/A ratio, E's (m/sec): early diastolic relaxation velocity, E/E' ratio and LA size was taken. Left Ventricular Mass Index was calculated by the Devereux formula: LVMI=[0.8{1.04[([LVIDD + IVSD +LVPWD]3-LVIDD3)]+0.6]/body surface area[8].

Results

Among all 60 patients, 31.7% patients were ≤40 years of age and 18.3% were >60 years of age. The mean (SD) age was 48.2(12.4) years. 39(65%) patients were male and 21(35%) were female patients. Among all study participants, majority (61.7%) had multiple co-morbidities. Hypertension was the most common co-morbidity (88.3%) followed by diabetes (60%). The mean (SD) SBP and DBP were 138.7(19.4) mm Hg and 84.5(11.3) mm Hg.

Table 1 depicts that Diastolic Dysfunction was present in 83.3% patients. Majority (41.6%) of the patients had grade II Diastolic Dysfunction; among this group, it was highest in stage IV CKD patients. Grade III diastolic dysfunction was present in 20% of total patients and it was highest (66.7%) among stage V CKD patients. There was significant association (P value<0.001) and spearman Rho correlation was 0.693; significant positive correlation was noted.

As shown in Table 2, 76.7% patients have normal

Table 1 — *CKD stages and LV Diastolic Dysfunction*

LVDD	Stages of CKD						Chi Square, df, P Value
	G1 No (%)	G2 No (%)	G3 No (%)	G4 No (%)	G5 No (%)	Total No (%)	
Normal	4 (80)	3 (33.4)	1(7.6)	1 (6.2)	1 (5.9)	10 (16.7)	
Grade I	1 (20)	4 (44.4)	6(46.4)	1(6.2)	1 (5.9)	13 (21.7)	55.2,
Grade II	0 (0)	2 (22.2)	5 (38.4)	11(68.8)	7 (41.1)	25 (41.6)	12, <0.001
Grade III	0 (0)	0 (0)	1(7.6)	3(18.8)	8(47.1)	12 (20)	
Total	5 (100)	9 (100)	13 (100)	16 (100)	17 (100)	60 (100)	

¥ Spearman Rho Correlation Coefficient (P value) = 0.693 (<0.001)

LVEF (systolic function); 16.7% patients had mildly abnormal Systolic function. There was significant association and moderate but significant correlation between Systolic Dysfunction and advanced stages of CKD.

Table 3 shows the mean along with standard deviation for E/A, E/E', LA diameter, LVMI, %FS, EF in different stages of Chronic Kidney Disease. The mean E/E' increased from 5.96(SD0.51) in CKD stage 1 to 13.67(SD 1.78) in CKD stage 5; the mean E/A decreased from 1.08 (SD 0.17) in CKD stage 1 to 0.83 (SD 0.25) in CKD stage 2 and then increased to 1.73(SD 0.52) in CKD stage 5. LA diameter progressively increased with a mean 33.94(SD 3.8) to 53.98(SD 6.88) in CKD stage 5. LVMI shows similar progression with 99.4(SD 6.37) in CKD stage 1 to 146.87(SD 18.95) in CKD stage 5.FS (%) and EF(%) shows a similar decrement with advanced stages; mean values are 43.08(SD 1.08) in stage 1 to 22.29(SD 6.53) in stage 5 and 64.6(SD 1.62) in CKD stage 1 to 45.56(SD 9.31) in CKD stage 5 for FS(%) and EF(%) respectively. Concentric LVH was more prevalent (75%) in stage 2 and eccentric LVH was more seen in end stages (87.4%).

Discussion

Our study was a hospital-based cross-sectional study conducted in patients attending Nephrology and General medicine OPD and IPD, Medical College, Kolkata.

Left Ventricular Systolic Function (LVSF) was measured using Left Ventricular Ejection Fraction (LVEF), Fractional Shortening (FS) and regional wall motion abnormality (RWMA). Of all the patients, 76.7% patients have normal LVEF(systolic function). Among patients with severely abnormal LVSF, one patient belonged to stage IV and another patient was in stage V. 88.3% of stage IV patients had normal LVSF. 50% of stage V patients had mildly abnormal LVSF followed by normal LVSF in 31.3% in the same group. There was a significant association and moderate but significant correlation between gradually increasing systolic dysfunction and progressing stages of CKD. The study by Szu-Chia Chen, *et al*

Table 2 — *CKD stages and LV Systolic Dysfunction*

LVEF % (Systolic Dysfunction)	Stages of CKD						Chi Squared, df, P Value
	G1 No (%)	G2 No (%)	G3 No (%)	G4 No (%)	G5 No (%)	Total No (%)	
Normal	5 (100)	8 (100)	13 (100)	15 (83.3)	5 (31.3)	46 (76.7)	
Mildly abnormal	0 (0)	0 (0)	0 (0)	2 (11.1)	8 (50)	10 (16.7)	28.63,
Moderately abnormal	0 (0)	0 (0)	0 (0)	0 (0)	2 (12.1)	2 (3.3)	12, 0.004
Severely abnormal	0 (0)	0 (0)	0 (0)	1 (5.6)	1 (6.3)	2 (3.3)	
Total	5 (100)	8 (100)	13 (100)	18 (100)	16 (100)	60 (100)	

¥ Spearman Rho Correlation Coefficient (P value) = 0.596 (<0.001)

Table 3 — *Echo measures of LV Systolic and Diastolic Dysfunction in different stages of CKD*

	Chronic Kidney Disease					
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Rho P value
E/A	1.08(0.17)	0.83(0.25)	0.97(0.48)	1.62(0.38)	1.73(0.52)	0.599 P<0.001
E/E'	5.96(0.51)	7.34(0.59)	10.58(1.58)	13.30(1.21)	13.67(1.78)	0.841 P<0.001
LA Diameter	33.94(3.8)	33.94(3.09)	43.88(3.16)	50.05(5.07)	53.98(6.88)	0.549 P<0.001
LVMI	99.4(6.37)	112(10.42)	120.46(11.88)	132.72(19.70)	146.87(18.95)	0.369 P<0.001
Fractional Shortening	43.08(1.08)	39(1.44)	33.41(2.17)	29.44(5.25)	22.29(6.53)	-0.691 P<0.001
LVEF%	64.6(1.62)	64(1.41)	62.76(5.63)	55.33(0.66)	45.56(9.31)	0.596 P<0.001
Concentric LVH	1(20%)	6(75%)	9(69.2%)	9(50%)	1(6.3%)	
Eccentric LVH	0(0%)	0(0%)	0(0%)	6(33.3%)	14(87.4%)	

reported a significant trend of stepwise decrease in LVEF with the advancement of CKD stages[9]. A study was done by Farah Anum Jameel, *et al* showed left ventricular systolic dysfunction was present in 31% of end-stage renal disease patients[10]. A similar study done by Mukesh Laddha, *et al* reported reduced ejection fraction among 24.3% of patients with end-stage renal disease[11]. The study done by Chelliah Dharmaraj, *et al* also showed systolic dysfunction among 34% of CKD patients[12]. In our study, 28.3% patients had below normal fractional shortening. A majority(77%) of patients with below normal fractional shortening belonged to stage V CKD. Significant association was noted between stages of CKD and fractional shortening. Spearman Rho correlation coefficient value was -0.691 that is, significant negative correlation was present. The study done by Rathod Nitin R, *et al* reported 29% patients with mild/moderate CKD (eGFR>30ml/min/1.73m^2) and 21.7% of severe CKD (eGFR<30 ml/min/1.73m^2) had impaired (≤25%) fractional shortening[13]. We found no regional wall motion abnormality in 70% patients. Mild global hypokinesia was present in 18.3% patients and most of them were in stage V CKD. Severe global hypokinesia was present in 11.7% patients and 72% of them were in stage V CKD. Significant association (P value <0.001) was noted between stages of CKD and RWMA and there was moderate and positive correlation (P value 0.574). The study by Reetu*Gupta et al* studied 100 CKD patients and the study reported: 17.1% of stage 2 CKD cases had preserved ejection fraction and 64.3% of stage 2 CKD cases were having reduced ejection function[14]. 35.7% of stage 3 CKD cases had preserved ejection fraction and 64.7% of stage 3 CKD cases were having reduced ejection function 35.3% of stage 4 CKD cases had preserved ejection fraction and 64.7% of stage 4 CKD cases were having reduced ejection function. 22.6% of stage 5 CKD cases had preserved ejection fraction and 77.4% of stage 5 CKD cases were having reduced ejection function. The prevalence of systolic dysfunction as indicated by reduced ejection fraction was increasing with CKD stages which was similar to our study. In this study, the mean Left Ventricular Mass Index (LVMI) was 127.7 gm/m^2 with standard deviation of 22.3 gm/m^2. 88.3% of patients had increased LVMI; among them, the majority belonged to stage IV followed by stage V and stage III respectively. A significant positive correlation was present between stages of CKD and LVMI (P value<0.001; Spearman correlation coefficient =0.369). The study done by Szu-Chia Chen, *et al* reported a significant trend for stepwise increase in LVMI and the prevalence of left ventricular hypertrophy corresponding to the advancement of CKD stages[9]. LVMI was further categorized with respect to relative wall thickness and we found 43.3% patients had concentric LVH; 33.3% of patients had eccentric LVH and 23.4% had concentric remodeling. 70% of patients with eccentric LVH were in stage V. Concentric LVH prevalence increased with advancement of stages of CKD up to stage IV in our study. No significant correlation was found between stages of CKD and categories of LVMI. Park, *et al* measured LV mass for LVH and found linear correlation and significant association between LV mass and worsening kidney function[15]. In this study cohort, 13% of patients had eccentric hypertrophy, 36% patients had concentric hypertrophy, 30% had concentric remodeling and 21% had normal LV geometry. The study done by Rathod Nitin R, *et al* reported the incidence of LVH in 40% of CKD patients and 40 % of LVH was concentric type and 60% was an eccentric type[13]. In our study, 83.3% patients had diastolic dysfunction. This finding is comparable to a similar study by Chelilah, *et al* where diastolic dysfunction was present in 74% patients[12]. In the CRIC study (stage 2-4 CKD) diastolic function was abnormal in 71% of patients[15]. In our study population, among the patients with CKD stage I, 80% had no diastolic dysfunction. Majority (41.6%) of the patients had grade II diastolic dysfunction; among this group, it was highest in stage IV CKD patients. Grade III diastolic dysfunction was present in 20% of total patients and it was highest (66.7%) among stage V CKD patients. A head on comparison was done between stages of CKD and grade of diastolic dysfunction with Chi square test. There was significant association (P value <0.001) and spearman Rho correlation was 0.693; significant positive correlation was noted that is increase in diastolic dysfunction with progressive stages of CKD. The mean value of E/A and E/E' increased progressively with advanced stages of CKD and it was statistically significant and positively correlated. This finding is comparable to the study done by Beata Franczyk, *et al*; this study found that LA size and E/E' increases significantly in later stages of CKD and also E/E' is the best predictor of Diastolic Dysfunction[16]. In a similar study, Takenori Otsuka, *et al* found that severity of kidney dysfunction increased significantly in parallel with the rise of E/E' (P<0.02), which is corroborative with our study[17]. The study done by Shady Elhusseiny, *et al* found significant direct correlation between GFR and E/MED

E' and LAT E'. There was significant inverse correlation between GFR and LA size , E/A and grades of LVDD[18]. In our study, LVH (concentric and eccentric) was present in 76.6 % patients; LV systolic dysfunction was present in 23.3% patients and LV diastolic dysfunction was present in 83.3% patients. A similar study by Ahmed, *et al* reported LVH in 80% patients; LV Diastolic Dysfunction in 53.3% patients and LV Systolic Dysfunction in 36.3% patients[19]. LVSF and LVH findings were corroborative to this study. Another study by Laddha, *et al* reported LVH in 74.3% patients, diastolic dysfunction in 61.4%, systolic dysfunction in 24.3% patients[11]. The higher percentage of diastolic dysfunction in our study may be due to selection bias. In the study done by. Chillo P, *et al* prevalence of LV systolic dysfunction was 16.2%[20]. Most of the patients were having ESRD.In our study, all the echocardiographic parameters were individually correlated with urine ACR and eGFR separately by Spearman Rho correlation coefficient. With urine ACR significant positive correlation was found with LVEF%, fractional shortening, negative correlation was found with LVIDd, LVIDs, LVMI, RWMA, E/E' ,E/A ratio, LA diameter and grades of LV diastolic dysfunction. In a study conducted by Hiraki Nagai, *et al* it was found that urine ACR even at low level can be associated with significant diastolic dysfunction which corroborates with our study[21]. eGFR had significant positive correlation with fractional shortening, LVEF; significant negative correlation LVIDd, LVIDs, E/A, E/E' ratio, LVMI, LA diameter and RWMA and grades of LVDD. A similar study done by K Matsushita, *et al* found lower eGFR and higher albuminuria were associated with increased LV mass, size, and systolic and diastolic dysfunction[22]. Association with systolic dysfunction was weaker than other LV parameters. The associations with eGFR were most evident at level <30ml/min/1.73m^2 whereas even a high normal ACR of 10-29 mg/g demonstrated significant association with some cardiac abnormalities. Findings of association with eGFR corroborated with our study. Masugata, *et al* in a similar study has found that E/E' increases with decreasing eGFR which is like the finding of this study[23]. In a similar study by Tarun Rao, *et al* showed that the prevalence of LV systolic dysfunction (Odds Ratio for Stage II was 1.8 and for stage V was 3.29) and LV diastolic dysfunction (Odds Ratio for stage II was 2.24 and for stage V was 6.6) increased with more severe renal dysfunction[24]. The mean EF decreased from 55.8 in CKD stage I to 53.1 in CKD stage 5, a similar finding was for fractional shortening. The mean E/A increased from 1.15 in CKD stage I to 1.67 in CKD stage V. The mean E/E' ratio increased from 9.1 in stage I to 11.8 in CKD stage V. Our study findings corroborated with this study.

Conclusion

Our cardinal effort in this study was to evaluate cardiac function in different stages of Chronic Kidney Disease with the help of 2D echocardiography in our Tertiary Care Hospital. In 60 diagnosed CKD patients of different stages participated in our study. In our study, LVH was the most common (76%) cardiac structural abnormality. LV diastolic dysfunction was present in 83.3% of patients and LV Systolic Dysfunction was present in 23.3% of patients. With advanced stages of CKD, there was a statistically significant increase in Left Ventricular Diastolic Dysfunction, Left Ventricular Mass Index and a statistically significant decrease in fractional shortening, LV Systolic Function. Estimated GFR also had a significant positive correlation with fractional shortening and a significant negative correlation with LVMI, LV diastolic dysfunction, and LV systolic dysfunction. In our study, we also found a significant positive correlation between urine ACR with fractional shortening and a significant negative correlation with LVMI, LV systolic dysfunction, and LVDD. LV diastolic dysfunction is present from the early stages of CKD. LV systolic function remains preserved till later stages and in our study, we found decreased LV systolic function from stage IV onwards. There is an increased prevalence of concentric hypertrophy in the early stages of CKD while eccentric hypertrophy was present mostly in stage V followed by stage IV. It may be possible to use eGFR and urine ACR as a predictive markers of worse cardiac function in CKD patients if they are properly followed up. Echocardiography should be used as an essential investigation for cardiac function evaluation in CKD patients in all stages.

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