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Echocardiography Based Assessment of Cardiac Function in Patients With Reno-cardiac Syndrome

Nadia Shams, Muhammad Hussain Baloch, Furquana Niaz, Lubna Meraj, Mubarak Ali

ABSTRACT

Objectives: There is rising world-wide burden of chronic kidney disease (CKD) with high Cardio-vascular mortality. This research aims to study echocardiography based cardiac function with respect to CKD stages.

Study Design and Setting: This cross-sectional study was conducted at RIHS Islamabad (Jan 2021–Jan 2022) after ethical approval.

Methodology: Total 130 adult CKD cases were included by consecutive sampling. Acute kidney injury and diagnosed/treated cases of cardiac disease were excluded. BMI and GFR was calculated. CKD staging done by KDOQI-classification. Cardiac impairment categorized by ECG and Echocardiography. Data analyzed by SPSS V-22 with Chi-square test.

Results: Amongst 130 CKD cases, there were 66(51%) males and 64(49%) females. Mean age was 60+13.27 years, mean BMI was 24+4.2. Diabetes mellitus was observed in 100(76.9%), hypertension in 122(93.8%). Mean creatinine was 4.83mg/dl and mean GFR was 17.84 mL/min/1.73m^2. Twenty-five(19.2%) patients were on hemodialysis. Mean cardiac EF was 49.18%**.** EF was normal in 39(30%), mildly reduced in 40(30.8%), moderately reduced in 29(22.3%) and severely reduced in 22(16.9%), diastolic dysfunction seen in 08(6.2%). Twenty-five(18.5%) cases had congestive cardiac failure; 14(56%) compensated and 11(44%) decompensated CCF. There was significant association between GFR and EF ($p<0.0001$).

Conclusions: Decline in cardiac function is associated with advanced CKD stages. Cardiac evaluation suggested at initial presentation of CKD, hence diagnosing asymptomatic compensated heart failure. Study finds high burden of diabetes, hypertension, anemia and IHD in CKD cases. GFR should be used rather than isolated creatinine in CKD. High clinical suspicion and early intervention may lead to better outcome.

Key Words: Chronic Kidney disease, Estimated Glomerular filtration rate, Reno-cardiac Syndrome, KDOQI classification.

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INTRODUCTION:

Chronic Kidney Disease (CKD) is presence of structural and functional kidney damage for >3 months, irrespective of cause.[1] Patients with CKD frequently experience cardiovascular and other co-morbidities.[2] Global burden of CKD is on rise with estimated prevalence 8-16%.[3] A community-based study conducted in Karachi in 2014 reported CKD prevalence of 12.5%.[4] However, higher prevalence of 29.9% observed in a south-Asian study by Jafar et al.[5]

CKD is an inflammatory state with various implications, especially on microvasculature.[6] Cardio-renal axis plays role in maintaining effective extracellular circulating volume. Equilibrium is maintained by various mechanisms i.e., volume/pressure sensors, neurohormonal feedback loops, vasoactive substances, transporters, rennin-angiotensin-aldosterone system, endothelin's, arginine, vasopressin & natriuretic peptides.

Reno-cardiac syndrome (RCS) is defined as CKD leading to progressive secondary cardiac dysfunction. including structural abnormalities like fibrosis, left ventricular (LV) hypertrophy or functional changes like ischemia, arrhythmia and systolic/diastolic dysfunction. There is no single diagnostic biomarker or imaging modality for RCS. Hence, the most common inclusion criterion is underlying CKD or

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ESRD with coexisting cardiac pathology.[7,8]

Leading cause of mortality and morbidity across spectrum of CKD is overwhelming cardiovascular disease having higher risk association with microalbuminuria or reduced GFR. Cardiovascular disease in CKD manifest in variety of ways like atherosclerosis, arteriosclerosis, LV hypertrophy, reduced LV contractility, impaired LV relaxation, pericardial effusion, aortic & mitral valve disease, mitral annular calcification, endocarditis, atrial fibrillation and ventricular arrhythmias that may lead to sudden cardiac death. There is higher incidence of both ischemic and hemorrhagic events than general population. Not surprisingly, cardiovascular disease is also associated with cerebro-vascular manifestations in CKD cases, including cognitive decline.

Approximately 50% mortality in end stage renal disease (ESRD) is attributed to cardiovascular events, including myocardial infarction, sudden cardiac death, arrythmias and cardiomyopathy.[9] The electrolyte imbalances, in particular hyperkalemia, associated co-morbidities i.e., diabetes, hypertension and dyslipidemia also attribute to cardiovascular morbidity and mortality in CKD.

Data from this study will highlight importance of cardiac evaluation in CKD cases. Hence, timely screening and intervention for reno-cardiac syndrome may reduce the mortality and morbidity. This may guide us regarding protocols of cardiac evaluation in CKD and identifying high cardiovascular risk cases that need to be evaluated and intervened.

METHODOLOGY:

This cross-sectional study was conducted at Dept. of Medicine and Nephrology at Rawal Institute of Health Sciences Islamabad from 1st January 2021 to 1st January 2022. Research was conducted after ethical approval by research and ethics committee of RIHS (ERC# RIHS-REC/056/20).

The 130 diagnosed adult CKD patients (age>18 years) of both the genders were included. Acute kidney injury, previously diagnosed or treated cases of cardiac impairment and patients with <3 months history of renal impairment were excluded. The CKD cases were selected by consecutive sampling and informed consent was obtained. Demographic data, detailed history and clinical examination findings were documented. Height and weight of the patients was recorded and body mass index (BMI) was calculated by formula weight(kg)/ height (m^2).

The serum creatinine levels were obtained. Estimated GFR was calculated by Modification of Diet in Renal Disease (MDRD) formula.[1] The staging of CKD was done by Kidney Disease Outcomes Quality Initiative (KDOQI) classification by national Kidney Foundation.[2] Patients were categorized into CKD stage 1 – 5.

The cardiac evaluation was done on the basis of history, clinical examination, electrocardiography (ECG) and Echocardiography. The degree of cardiac impairment was categorized. Ischemic heart disease was labelled on the basis of history along with ECG, ETT or angiography findings in individual cases.

Data was entered on a specially designed proforma and analyzed by SPSS V-22. Frequencies and percentages were calculated for qualitative variables (i.e., gender, CKD stage); mean and standard deviation were calculated for quantitative variables (age, creatinine, BMI, GFR and cardiac ejection fraction). Chi-square test applied as a test of significance to study the association of eGFR with cardiac ejection fraction. *P-value <0.05* was considered as statistically significant. Data presented as tables and bar graphs.

RESULTS:

Amongst 130 chronic kidney disease cases included in this study, there were 66(51%) males and 64(49%) females. Mean age was 60±13.27 years with a range of 30-87 years. Mean BMI was 24±4.2. Mean monthly income was 25,769±11,676 (10,000-60,000) rupees. Twenty (15.4%) cases were employed, 04(3.1%) were retired and 106(81.5%) were un-employed (table 1).

The most common co-morbid condition observed was hypertension i.e., 122(93.8%), ischemic heart disease in 106(81.5%), diabetes mellitus type 2 in 100(76.9%), congestive cardiac failure in 24(18.5%), Hepatitis C in 13(10%), Hepatitis B and HIV in none of the cases (fig 1).

Various laboratory parameters including mean hemoglobin, renal function tests and electrolytes are presented in Table 1. Mean creatinine level was 4.83±3.53 mg/dl (range 1.2-16) and mean urea was 123.87±66.57 mg/dl (range 39-364). The mean Glomerular filtration rate (GFR) was 17.84±11.33 (2.85-45.18). Total 25(19.2%) patients were receiving the hemodialysis therapy. According to stage of CKD, 73(56.2%) cases were in CKD stage 5, 32(24.6%) cases in CKD stage 4, 22(16.9%) in CKD stage 3 and 03(2.3%) in stage 2. However, we didn't have any patient in CKD stage 1 (table 2).

The mean ejection fraction (EF) of the heart in CKD cases based on echocardiography was 49.18+12.54 % (range 25-65). EF was found to be normal in 39(30%) CKD cases, mildly reduced in 40(30.8%), moderately reduced in 29(22.3%) and severely reduced in 22(16.9%) CKD cases (table 2). Diastolic dysfunction was found in 08(6.2%) CKD patients.

Total 25(18.5%) cases of CKD were diagnosed to have congestive cardiac failure on the basis of history, clinical examination and investigations. Amongst these, 14(56%) cases had compensated CCF and 11(44%) had decompensated CCF. There was significant association between glomerular filtration rate and ejection fraction of the heart ($p<0.0001$).

Table 1: Presenting the demographic variables, anthropometric measurements, electrolytes, renal and cardiac functions (n=130)

Variables		**Mean + SD** (n=130)	**Range**
Age (years)		60.2 ± 13.27	30-87
Monthly income (Rs)		25,769 ± 11,676	10,000-60,000
Height (feet)		5.53 ± 0.247	5-5.8
Weight (kg)		65.18 ± 12.51	40-98
BMI (kg/m^2)		24.27 ± 4.27	17.08-37.55
BP systolic (mmHg)		137.05 ± 20.15	90-180
BP diastolic (mmHg)		83.42 ± 12.49	60-110
Laboratory parameters	Hemoglobin (gm/dl)	10.0 ± 1.65	5.9-14.0
	MCV (fl)	81.28 ± 6.25	60-93
	Urea	123.87 ± 66.57	39-364
	Creatinine	4.83 ± 3.53	1.2-16
	Sodium	131.57 + 15	19-142
	Potassium	4.66 + 0.82	2.3 -7.5
	Calcium	8.84 + 0.72	7.0 – 10.1
	Phosphorus	5.03 + 1.36	2.5-9.4
GFR		17.84 + 11.33	2.85-45.18
Ejection fraction (%)		49.18 + 12.54	25-65

Table 2: Presenting the Ejection fraction grades in various CKD stages (n=13)

CKD Stage	**Normal** (>55%) n=39	**Mildly reduced** (41-55% EF) n=40	**Moderately reduced** (30-40% EF) n=29	**Severely reduced** (<30% EF) n=22	**P-value**
2	**02**	**01**	**00**	**00**	*0.035*
3	**12**	**06**	**02**	**02**	
4	**08**	**15**	**06**	**03**	
5	**17**	**19**	**20**	**17**	

Test of significance Chi-square test; significant p<0.05

Table 3: Presenting the mean GFR and the mean Ejection fraction in CKD cases (n=130)

Variable	**Mean ± SD (n=130)**	**Range**	*P-value*
Glomerular Filtration rate	17.84 ± 11.33	2.85-49.18	*<0.0001*
Ejection Fraction (%)	49.18 ± 12.54	25-65	

Test of significance Chi-square test; p<0.05 significant

Figure 1: Pie Chart presenting the co-morbid conditions in chronic kidney disease cases (n=130).

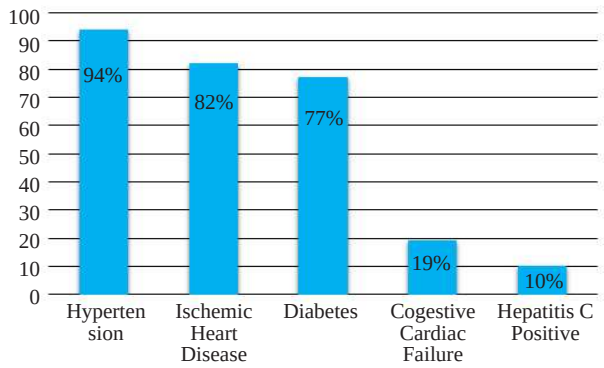
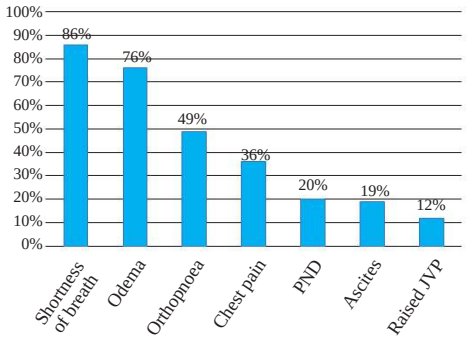


Figure 2: Bar graph presenting various symptoms and signs observed in CKD cases (n=130).



DISCUSSION:

This study finds significant association between left ventricular systolic ejection fraction (LVEF) and the estimated glomerular filtration rate (eGFR). The mean age of the study participants was sixty years with a range of youngest patient of thirty years age and eldest patient eighty-seven years old. Majority of the patients were above fifty years, reflecting the age-related distribution of CKD. Younger patients may develop CKD secondary to congenital hypoplastic kidneys, obstructive uropathy, glomerulonephritis, etc. Certain co-morbid conditions like diabetes, hypertension, pre-renal and post-renal etiologies also lead to CKD.[12]

The body mass index (BMI) was calculated with aim to calculate the eGFR. The mean BMI was twenty-four. Very few CKD cases were overweight or obese. This may be explained by contributory factors like anorexia, ill health, gastro-intestinal malabsorption from gut, loss of muscle mass and wasting in CKD cases.[13] The quality of life needs to be improved by appropriate dietary advise to maintain an appropriate weight in CKD cases. The dietary restrictions and electrolyte abnormalities to be kept in mind while individualizing the diet and caloric intake.[14]

Ten percent of the cases were hepatitis C positive, while none was Hepatitis B positive. The active immunization has contributed to the decline in hepatitis B in our patients. Hepatitis-B immunization is recommended in CKD cases in view of repeated intravenous samplings, intravenous medications and hemodialysis. As these factors increase the risk of exposure to hepatitis B, Hepatitis C and HIV.

Diabetes mellitus has been a predominant contributory factor for CKD in our region. Diabetic nephropathy has been a frequently observed microvascular complication of diabetes. The point to be focused is that with good glycemic control and other preventive measures, the diabetic nephropathy can be avoided or delayed.[15] Approximately seventy seven percent of our cases had diabetes mellitus. This reflects the contribution of diabetes to CKD.

More than ninety percent of our cases were hypertensive. Hypertension and CKD may have varied temporal

association. The hypertension and CKD bear an overlapping cause and effect relationship. Certain cases have hypertensive renal disease leading to CKD. On the other hand, some cases develop hypertension as a consequence of CKD.[16] In either of these situations' early diagnosis and appropriate management of hypertension delays the onset or progression of the CKD. Despite the history of hypertension, most of our patients had therapeutically optimized blood pressures.

Renal anemia is one the most frequent complication of CKD. It involves the decreased endogenous erythropoietin. Most of the study subjects had normochromic normocytic anemia. The KDIGO guidelines state that hemoglobin levels in CKD cases shouldn't be raised above 13gm/dl and the erythropoietin therapy is recommended at hemoglobin < 10 gm/dl, with target hemoglobin 10-11.5 gm/dl.[17]

The gold standard for determining renal functions is GFR.[18] Certain formulas are used worldwide to estimate renal functions including the Cockcroft-Gault formula to estimate the creatinine clearance (CrCl) and, the Modification of Diet in Renal Disease (MDRD) to estimate the glomerular filtration rate (e-GFR).[10] As per the Staging of CKD according to estimated GFR, more than half of our patients were in CKD stage 5 and almost 1/4th in CKD stage 4. We had fewer cases in CKD stage 3 and only three cases in CKD stage 2. The reason may be delay in approach or referral to tertiary healthcare or nephrology. Many patients are referred when the creatinine is already markedly deranged. Hence, authors take the opportunity to convey message from this research that GFR should be calculated for each case of CKD. GFR should be used as basis to evaluate renal function rather than isolated creatinine levels as isolated creatinine may overestimate the renal functions.

While comparing the CKD stages with the cardiac function based on echocardiography-based ejection fraction, we found that more than half of the CKD stage 5 cases had reduced EF. Similarly, reduced EF was found in 3/4th of CKD 4, half of CKD 3 and 1/3rd of CKD 2 cases. There was significant association between the GFR based CKD stage and decline in ejection fraction of heart. Among all cases, thirty percent were found to have preserved ejection fraction vs. seventy percent had reduced ejection fraction. This figure is comparatively higher as compared to Karachi based study by Jameel et al that found low ejection fraction in 31% hemodialysis cases.[19]

The concept is of heart failure with preserved ejection fraction also needs to be discussed. The study conducted by Mavrakanas et al found higher risk of admission in CKD cases having heart failure with preserved ejection fraction (i.e., EF>50%).[20] Hence, this strengthens the recommendation to screen all CKD cases for cardiac dysfunction. This can be done by clinical examination supported by ECG and echocardiography; particularly in CKD stage 3 and above. The earlier stages of CKD should also be monitored as timely intervention may help preserving the cardiac function, hence avoiding the cardiovascular events in CKD cases.

Another interpretation in this study was that amongst cases of heart failure, more than half had compensated heart failure. These cases might not be having overt or obvious symptoms of heart failure and hence their diagnosis of heart failure may be missed. The benefit of diagnosing heart failure will be initiation of preventive therapy for cardiac failure. This may prevent or delay the decline in cardiac function and avoid the cardiac decompensation, acute cardiac events or overt failure.

Certain limitations of the study include sampling technique and inability to perform certain advanced investigations due to financial constraints e.g., basal natriuretic peptides (BNP), cardiac catheterization. Also, we were unable to induct more CKD cases in stage 1 and 2. Hence, results of this study should be interpreted carefully with reference to early stages of CKD. Authors recommend further regional studies with improved sample size and in-depth cardiac evaluation in CKD cases.

CONCLUSION:

The decline in cardiac function is found to be associated with advanced stages of CKD. All the CKD cases are recommended to undergo cardiac evaluation at initial diagnosis and then accordingly at regular intervals. There is high burden of co-morbid conditions particularly diabetes, hypertension, anemia and ischemic heart disease in CKD cases from this region. GFR should be used to estimate the renal functions in CKD cases rather than isolated creatinine levels to avoid errors in the renal function estimation. It is important to diagnose the patients in compensated heart failure and without overt symptoms. This needs high clinical suspicion, supported by investigations. Early intervention may lead to better outcome and reduce the morbidity and mortality.

Authors Contribution:
Nadia Shams: Study design, data collection, write up, data analysis
Muhammad Hussain Baloch: Data collection, write up
Furquana Niaz: Data collection, literature review, write up
Lubna Meraj: Data collection, write up, referencing
Mubarak Ali: Data collection, data entry, write up

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