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Original Article

Cardiorenal syndrome type 4: A study of cardiovascular diseases in chronic kidney disease

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ABSTRACT

Introduction: The heart and the kidneys are tightly interlinked with each other. So, primary disorder of one of these organs often results in the secondary dysfunction of other. Such interactions play a vital role in the pathogenesis of a clinical entity called cardio-renal syndrome (CRS). CRS type 4 refers to the development of cardiac failure in the patients with CKD.

Objectives: To study the prevalence of various cardiac diseases in the patients with CKD and risk factors for it.

Methods: Eighty patients with CKD who were being treated at KIMS, Hubli, from 1st January 2015 to 30th June 2015 were selected. Clinical evaluation and relevant investigations including echocardiography were done.

Results: Mean age of study population was 43.50 ± 14.53 years. Heart failure with reduced ejection fraction (HFrEF) and Heart Failure with preserved ejection fraction (HFpEF) were present in 21 (26.25%) and 59 (73.75%) respectively. Left ventricular (LV) hypertrophy was present in 55(68.75%). Thus, the prevalence of CRS type 4 was 61 (76.25%). Pericardial effusion was present in 12 (15%). Complete heart block was present in 2 (2.5%). Pulmonary hypertension (PH) was present in 35 (43.75%). Mean central venous pressure (CVP) and interdialysis fluid retention were significantly greater among those with LV failure, compared to those without LV failure ($p = 0.0002$, $p = 0.025$ respectively). Mean hemoglobin was significantly lower among patients with LV failure, compared to those without LV failure ($p = 0.032$).

Conclusion: The prevalence of cardiorenal syndrome type 4 is substantially high in patients with CKD and carries adverse outcome in relation to patient management.

1. Introduction

Chronic kidney disease (CKD) has been increasingly recognized as a global health problem. More than 10% of the adults in the United States suffer CKD, of various stages.[1] Kidney disease is the 9th leading cause of mortality.[2] An Indian population-based study showed the crude and age-adjusted ESRD incidence rates at 151 and 232 per million population, respectively.[3]

The patients with CKD most of the times die from cardiovascular diseases than progressing to End Stage Renal Disease (ESRD). Cardiovascular diseases such as CAD (coronary artery disease), HF (heart failure), arrhythmia, and sudden cardiac death represent the leading causes of morbidity and mortality in the patients with CKD, increasing sharply as the patients approach ESRD. The pathophysiology includes a complex, bidirectional interaction between the heart and the kidneys and has been termed as *cardio-renal syndrome (CRS) type 4.*[4]

The term 'cardiorenal syndrome' has been used to emphasize the tight interaction between the cardiovascular and the renal systems in acute or chronic diseases. The definition encompasses different syndromes, all involving the heart and the kidney, "whereby an acute or chronic dysfunction of one organ leads to an acute or chronic dysfunction of the other".[2] CRS type 4 (also known as chronic renocardiac syndrome) refers to development of cardiac failure and cardiac complications in patients with CKD.[5,6]

There are limited studies reported on CRS type 4. Hence, this study was conducted in our institute, Karnataka Institute of Medical Sciences, a Government run Tertiary care center and Medical college at Hubli, Karnataka.

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2. Objectives

1. To know the prevalence of various cardiac diseases in the patients with CKD.
2. To identify the risk factors for cardiac diseases in CKD.

3. Designs and settings

It was a cross-sectional observational study conducted at Karnataka Institute of Medical Sciences, from 1st January 2015 to 30th June 2015. Eighty patients with CKD were considered for the study after explaining the objectives of the study. Informed written consent was taken from all of them. The study was conducted after obtaining the approval by the Institute Ethics Committee.

3.1. Inclusion criteria

1. CKD diagnosed based on 'KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of CKD'.
2. Those aged 18 years or more.

3.2. Exclusion criteria

1. Those who were not willing to participate in the study.
2. Age less than 18 years.
3. Valvular heart diseases.
4. Congenital heart diseases.
5. Pulmonary obstructive and restrictive diseases.
6. HIV-infected patients.
7. Chronic liver disease.
8. Connective tissue diseases.
9. Hypothyroidism and Hyperthyroidism.

4. Methods

4.1. Protocol

The history was obtained from the patients with CKD, with special reference to the symptoms of CKD and cardiac disease, risk factor for developing CKD, co-morbid conditions, duration of diagnosis of CKD, and duration of hemodialysis. Clinical examination was done with special emphasis on signs of CKD and cardiac diseases. Each subject underwent the following investigations: Renal function tests, liver function tests, serum electrolytes, fasting plasma glucose, postprandial plasma glucose, complete blood count, ultrasound abdomen, chest X-ray (CXR), electrocardiography (ECG), and echocardiography. Glomerular Filtration Rate (GFR) was estimated using Cockrault-Gault formula and staging of CKD was done.

USG abdomen was done to note for the size and echotexture of the kidney. It was also used to rule out hepatic disease and portal hypertension as they can independently affect cardiovascular system. CXR was done to rule out obstructive and restrictive lung diseases and to look for features suggestive of PH, pulmonary edema, pleural effusion, cardiomegaly, and pericardial effusion.

ECG was done to assess features of pulmonary hypertension (PH), right ventricular (RV) strain pattern, left ventricular (LV) strain pattern, ischemic heart disease (IHD), arrhythmia, and heart blocks. Echocardiography was done in all patients to evaluate chamber size, LV systolic dysfunction, LV diastolic dysfunction, pericardial effusion, and to estimate pulmonary artery systolic pressure (PASP).

Comparison was made between the two groups.
Group 1: CKD patients with LV failure.
Group 2: CKD patients without LV failure.

Comparison was made in relation to general characteristics, clinical features, ECG, and echocardiographic findings.

4.2. Statistical analysis

Descriptive and inferential statistical analysis had been carried out in this study. The continuous variables including age, BP, EF, etc. were expressed in terms of mean ± S.D. The categorical measurements were expressed in number (percentage). Significance was assessed at 5% level of significance ($p < 0.05$).

Student's *t*-test (two-tailed, independent) was used to find the significance of the study parameters on continuous scale between the two groups with presence and absence of LV failure (Inter group analysis) on metric parameters. Chi-square/Fisher Exact test was used to find the significance of study parameters on categorical scale between the two groups. Statistical analysis was done with the IBM SPSS version 20.

5. Results

5.1. General characteristics

Mean age of the study population was 43.50 ± 14.53 years (mean ± S.D.). Majority were of the age 31 years to 50 years (65%), which represents the productive age group of the society. Majority of the patients were in stage 5 CKD (Table 1).

5.2. Clinical findings

Breathlessness was the commonest symptom, which was present in 68 out of 80 patients (85%). Pedal edema was present in 65 out of 80 patients (81.25%) (Fig. 1).

Systolic hypertension and diastolic hypertension were present in 60 (75%) and 52 (65%) respectively (Table 2, Table 3).

5.3. Cardiac manifestations in CKD

HFrEF was present in 21 (26.25%) patients. HFpEF was present in 59 (73.75%) patients. Total prevalence of left heart failure was 61 (76.25%) patients, with HFpEF being more common than HFrEF.

LV hypertrophy was present in 55(68.75%) patients. PH was present in 35(43.75%) patients. Pericardial effusion was present in 12 (15%) patients (Table 4, Fig. 2). All the cardiac complications were predominantly seen in CKD stage 5 (Table 5).

Among patients with HFrEF, majority had mild LV systolic dysfunction – 17 (21.25%) (Table 6).

5.4. Pulmonary hypertension

Pulmonary hypertension (PH) was present in 35(43.75%). Majority of the patients had moderate PH. In CKD stage 3, it was present in 1 out of 3 (33.3%). In stage 4, it was present in 2 out

Table 1
General characteristics of the patients studied.

	Variables	Data
1	Age (years)	
	Mean ± S.D.	43.50 ± 14.53
	Range	18–70
2	Sex ratio (M:F)	50:30
3	Hypertension	60 (75%)
4	Diabetes mellitus	31 (38.75%)
5	Anemia	76 (95%)
6	CKD stages [No. (%)]	
	Stage 3	3 (3.75%)
	Stage 4	5 (6.25%)
	Stage 5	72 (90%)

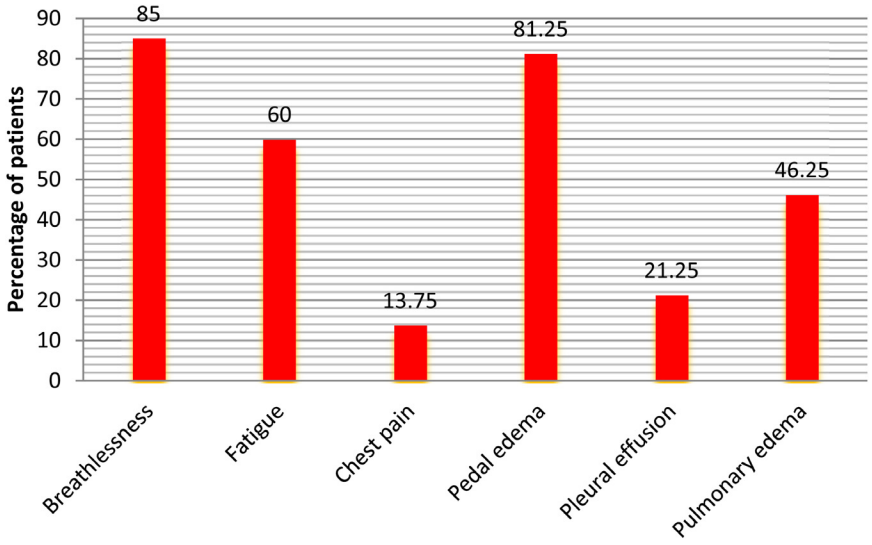

Fig. 1. Prevalence of various clinical findings in the patients studied.

Table 2
SBP in the patients studied.

Grading of SBP	SBP (mm Hg)	Total ($n = 80$)
Normal	<120	3 (3.75%)
Prehypertension	120–139	17 (21.25%)
Stage 1 hypertension	140–159	20 (25%)
Stage 2 hypertension	≥160	40 (50%)

Table 3
DBP in the patients studied.

Grading of DBP	DBP (mm Hg)	Total ($n = 80$)
Normal	<80	13 (16.25%)
Prehypertension	80–89	15 (18.75%)
Stage 1 hypertension	90–99	8 (10.0%)
Stage 2 hypertension	≥100	44 (55.0%)

Table 4
Echocardiographic findings in the patients studied.

ECHO findings	No. of patients (%)
HFrEF	21 (26.25%)
HFpEF	59 (73.75%)
LV hypertrophy	55 (68.75%)
PH	35 (43.75%)
Pericardial effusion	12 (15%)

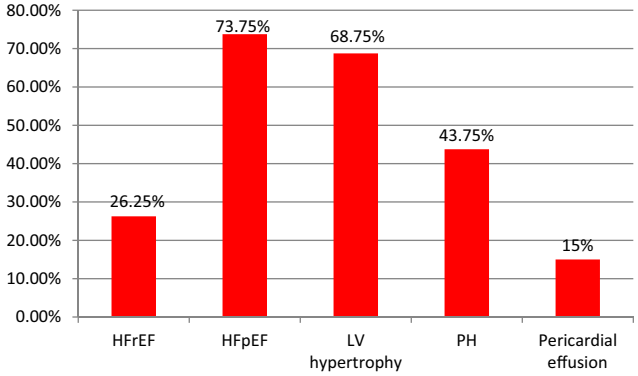

Fig. 2. Echocardiographic findings in the patients studied.

of 5 patients (40%). In stage 5, it was present in 32 out of 72 patients (44. 44%). This shows that with the progression of CKD, prevalence of PH also increases, although it is not statistically significant ($p = 0.716$) (Table 7).

5.5. Comparison between two groups

Clinical features such as breathlessness, pedal edema, and pulmonary edema were significantly more common among those with LV failure compared to those without LV failure (Table 8).

In ECG, the prevalence of left ventricular strain pattern and right ventricular strain pattern was significantly more among the patients with LV failure, compared to those without LV failure (Table 9).

Table 5
Comparison of echocardiographic findings in different stages of CKD.

Echocardiographic findings	Stages of CKD		
	3 ($n = 3$)	4 ($n = 5$)	5 ($n = 72$)
LV hypertrophy	0	2 (40%)	53 (73.61%)
HFrEF	0	1 (20%)	20 (27.78%)
HFpEF	1 (33.33%)	2 (40%)	56 (77.78%)
Pericardial effusion	0	0	12 (16.66%)

Table 6
Grading of HFrEF based on EF in the patients studied.

Grading of HFrEF	EF (%)	No. of patients (%)
Normal	≥55	59 (73.75%)
Mild	45–54	17 (21.25%)
Moderate	30–44	4 (5%)
Severe	<30	0 (0%)

Table 7
PH in different stages of CKD.

PH grades	PASP (mm Hg)	Stage of CKD			Total
		3	4	5	
Absent	<35	2	3	40	45
Mild	35–49	1	1	14	16
Moderate	50–69	0	1	17	18
Severe	≥70	0	0	1	1
Total		3	5	72	80

Table 8
Comparison of clinical features between the patients with presence and absence of LV failure.

Clinical features	LV failure		Total ($n=80$)	p value
	Present ($n=61$)	Absent ($n=19$)		
Breathlessness	59	9	68	**0.0001***
Fatigue	40	8	48	0.106
Chest pain	10	1	11	0.444
Pedal edema	56	9	65	**0.0001***
Pleural effusion	14	3	17	0.749
Pulmonary edema	35	2	37	**0.004***

* Statistically significant at $p > 0.05$.

Table 9
ECG findings in relation to presence or absence of LV failure.

ECG findings	LV failure		Total ($n=80$)	p value
	Present ($n=61$)	Absent ($n=19$)		
P pulmonale	1	0	1	1
Left ventricle strain	50	2	52	**0.014***
Ischemic heart disease[a]	4	0	4	0.56
Right ventricular strain	13	0	13	**0.030***
Complete heart block	2	0	2	1

[a] IHD was diagnosed based on present and past ECG and echo records. Invasive modes like Coronary angiography were not done in them.
* Statistically significant at $p > 0.05$.

Mean ± S.D. of SBP and DBP were greater among the patients with LV failure compared to those without LV failure ($p = 0.0013$ and $p = 0.0036$ respectively). This implies that the pressure overload is associated with increased risk of LV failure (Table 10).

Mean ± S.D. of CVP and interdialysis weight gain were significantly higher among the patients with LV failure compared to those without LV failure ($p = 0.0002$ and $p = 0.05$ respectively). This implies that the volume overload is associated with increased risk of LV failure (Table 10).

Duration of CKD and hemodialysis was longer among the patients with LV failure compared to those without LV failure, but it was not statistically significant.

Mean ± S.D. of hemoglobin among the patients with LV failure (7.01 ± 1.78) was significantly lower as compared to those without LV failure ($p = 0.032$). This implies that anemia is associated with increased risk of LV failure in CKD patients (Table 10).

6. Discussion

CKD patients have higher mortality, when compared to the general population, which is mainly attributed to cardiovascular events. Deaths due to cardiovascular events are far more common than progressing to ESRD and the need of renal replacement therapy.[7]

Proteinuria, whether considered as a marker of systemic endothelial dysfunction or a result of renal damage, has been associated with increased cardiovascular mortality.[8] In repeated studies, the presence of micro- and macroalbuminuria and GFR reduction were independent predictors of increased overall and cardiovascular mortality in both diabetic patients and non-diabetic patients.[9,10]

Irrespective of the presence of proteinuria, decline in GFR has been associated with increased cardiovascular morbidity and mortality. An inverse relationship between GFR and the severity of coronary artery stenosis was found as well as increased probability of having triple vessel disease with decreasing GFR.[11]

6.1. Pathogenesis of cardiorenal syndrome type 4

Several pathophysiological pathways have been identified to cause CRS type 4, including Renin-Angiotension-Aldosterone system (RAAS) activation, volume overload, osmotic sodium retention, endothelial dysfunction, anemia, dyslipidemia, coagulopathy, inflammation,[12] all leading to morphological alterations in the heart and vessels. In addition, other proposed mechanisms include sympathetic overactivity, non-osmotic sodium retention, cardiotonic steroids, and catalytic iron. Sympathetic activation by the failing kidney leads to both renal disease progression and cardiovascular morbidity.[12]

Risk factors for LV failure in CKD are traditional risk factors like hypertension, diabetes mellitus, hypercholesterolemia, age, smoking, obesity, and male sex.[13,14] Apart from these, non-traditional factors that have been implicated are anemia, inflammation, oxidative stress, endothelial dysfunction, circulating soluble receptor for advanced glycation end product (sRAGE), altered mineral metabolism, hyperparathyroidism, Fibroblast Growth Factor 23, asymmetric dimethyarginine, e-selectin, albuminuria, hyperuricemia, and arterial stiffness.[14]

A study by Joachim H. Ix et al. showed that higher serum cystatin C concentrations are strongly associated with LV hypertrophy and diastolic dysfunction.[15]

Vitamin D deficiency is quite prevalent among CKD patients, and it is associated with the high prevalence of myocardial dysfunction, heart failure, and sudden cardiac death.[16]

Nerpin et al. described the association between GFR and LV function in two independent community-based cohorts with no clinical evidence of heart failure, LV EF >40% and with GFR >60 mL/min per 1.73 m^2. The investigators observed a significant correlation between GFR and systolic, diastolic, and global LV function in both the studies.[17]

Table 10
Comparison of the characteristics between the groups with presence and absence of LV failure.

	LV failure		Total ($n=80$)	p value
	Present ($n=61$)	Absent ($n=19$)		
Age in years	44.09 ± 15.2	42.33 ± 11.20	43.50 ± 14.53	0.643
Pulse rate (bpm)	90.37 ± 13.24	90.17 ± 4.87	90.34 ± 12.33	0.949
SBP (mm Hg)	160.24 ± 24.89	136.17 ± 34.35	157.43 ± 26.62	**0.0013***
DBP (mm Hg)	94.88 ± 13.68	84.17 ± 13.14	93.88 ± 13.73	**0.0036***
CVP (cm H_20)	22.31 ± 7.12	15.33 ± 5.47	20.53 ± 7.07	**0.0002***
Interdialysis weight gain (kg)	3.11 ± 1.47	2.26 ± 1.22	2.81 ± 1.43	**0.025***
CKD duration (weeks)	47.01 ± 68.61	24.33 ± 32.35	43.57 ± 64.79	0.169
Hemoialysis duration (weeks)	28.87 ± 46.80	12 ± 14.23	26.30 ± 43.80	**0.127***
Hemoglobin (g/dl)	7.47 ± 2.09	8.6 ± 1.5	7.71 ± 2.04	**0.032***

* Statistically significant at $p > 0.05$.

6.2. Cardiac changes in CKD

LV hypertrophy is a common feature in CKD patients. It is attributable to both pressure overload and volume overload. Pressure overload is mainly derived from the increased peripheral vascular resistance and reduced arterial compliance due to sympathetic and RAAS overactivity, hypertension, endothelial dysfunction, and vascular calcification/stiffening. It causes thickening of cardiac myofibres by parallel addition of sarcomeres, thus leading to concentric LV hypertrophy.[18]

Volume overload is attributed to sodium and water retention, anemia, and the presence of an arteriovenous fistula in patients with ESRD.[18]

LV hypertrophy in renal disease is a pathologic process and is accompanied by fibrosis, which is also attributed to metabolic consequence of uremia, including increased parathyroid hormone, endothelin, aldosterone, catecholamines, and cardiotonic steroids.[10] Other histological changes of the heart in CKD include myocyte apoptosis/necrosis resulting in myocyte number reduction, and microvascular abnormalities such as arteriolar wall thickening and capillary rarefaction, the latter being specific to uremia.[4]

The consequences of above-mentioned structural changes include diastolic dysfunction, increased oxygen demand, and impaired myocardial oxygenation unrelated to coronary artery obstruction. This may explain the angiographic finding of patent coronary arteries in 30–40% of CKD patients with IHD.[19] These changes also explain their predisposition to arrhythmias and sudden death, which account for more than half of the cardiovascular mortality in them.[20] Susceptibility to arrhythmias and sudden death may be further increased by CAD/MI, CHF, LV hypertrophy, electrolyte abnormalities, anemia, autonomic imbalance, and inflammation.[20]

6.3. Vascular changes in CKD

Pathological features in CKD include thickening of the arterial wall, leading to an increased intima-media thickness and, vascular calcification.[21,22]. This leads to increased arterial pulse wave velocity.[23] Quite recently, the vascular calcification has become the focus of attention mainly because of its established association with cardiovascular mortality in CKD patients.[24]

6.4. LV failure in CKD

Avijit Debnath et al. have done an echocardiographic assessment of CKD patients. The assessment showed that 30% of total patients had LV systolic dysfunction, 15% among the patients with CKD stages 1–3, and 48% among the patients with CKD stages 4–5. LV hypertrophy was present in 58% among total study population, being prevalent in 33% and 87% among CKD stages 1–3 and stages 4–5 respectively.[25]

In comparison with the above study, in our study also, HFrEF (LV systolic dysfunction) was present in 26.25% of patients. HFpEF (LV diastolic dysfunction) was present in 77.75% of patients and LV hypertrophy in 68.75% of patients. In consistent with the above study, our study also shows that LV failure to be a predominant complication of ESRD.

In CKD patients, LV hypertrophy contributes to diastolic dysfunction, congestive heart failure, arrhythmia, and sudden death.[26] The prevalence of LV hypertrophy in the general population is 15–21%,[27] but it affects 50–70% of patients during intermediate stages of CKD and up to 90% of patients with ESRD.[28–30] In our study, LV hypertrophy was present in 40% of CKD stage 4 patients and 73.61% of CKD stage 5 patients.

6.5. Pulmonary hypertension in CKD

It is one of the overlooked complications of CKD, which has been estimated to be present in 27–58% of CKD patients in various studies.[31–35] It is an independent predictor of morbidity and mortality in them.[32,34]

In the first study of PH in CKD patients conducted by Yigla et al., the prevalence of PH in CKD patients was 39.7% and risk factors for developing PH were anemia and increased cardiac output.[31] Kumbar et al. found the prevalence of 42% in 36 patients of peritoneal dialysis and risk factors identified were dilated LV, lower EF and increased calcium× phosphate product. Fabbian et al. in their study found the prevalence of PH in 58.6% of patients on hemodialysis and 18.5% of peritoneal dialysis patients. All these studies demonstrate that LV failure is the predominant cause of PH in these patients, causing WHO group 2 PH.[32]

In consistent with these studies, PH was present in 43.75% of the patients in our study.

6.6. Anemia in CKD

Anemia is very common in CKD and contributes to cardiovascular disease. Various factors responsible for anemia, which include erythropoietin deficiency, diminished red cell survival, deficiency of iron, Vitamin B_{12} and folate due to malabsorption and anorexia, impaired coagulation and platelet function due to uremia, hyperparathyroidism, bone marrow fibrosis, and chronic inflammation.[36]

Robinson et al. conducted the study on prevalence of anemia nursing home residents and concluded that 59.6% of residents were anemic, and 43.1% had CKD, and residents with CKD were more likely to have anemia (64.9% with CKD vs 55.7% without CKD).[37] In our study, anemia had very high prevalence of 95% among CKD patients.

7. Conclusion

This study concludes that substantial number of patients with CKD suffers cardiovascular disease, i.e., Cardiorenal syndrome-type 4. HFpEF is more common than HFrEF. The risk factors for LV failure are anemia, volume overload secondary to fluid retention, and pressure overload secondary to systemic hypertension. Pulmonary hypertension is one of the recently recognized complications of CKD which is often overlooked. All these cardiovascular manifestations independently contribute to adverse outcome in these patients.

The high prevalence of LV failure on echocardiography implies that these patients require detailed cardiovascular evaluation despite absence of symptoms. Efforts targeted at prevention and control of LV failure and PH such as control of systemic hypertension, control of diabetes mellitus, correction of anemia, identification and treatment of IHD, achieving dry weight by setting an optimum ultrafitrate at hemodialysis, and optimal use of diuretics should be implemented as early as possible, to improve the treatment outcome of these patients.

8. Limitations of the study

1. The patients could not be followed up.
2. Impact of hemodialysis and correction of risk factors like anemia, systemic hypertension, diabetes mellitus, and volume overload on cardiac function could not be assessed.

Conflicts of interest

The authors have none to declare.

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