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

Suresh H. a, Arun B.S. b,*, Venkatesh Moger c, Mallikarjuna Swamy b

a Department of Cardiology, KIMS, Hubli, India
b Department of General Medicine, KIMS, Hubli, India
c Department of Nephrology, KIMS, Hubli, India

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). CRS type 4 refers to the development of cardiac failure in the patients with CKD.

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.

Article history:
Received 7 February 2016
Accepted 2 July 2016
Available online 15 July 2016

Keywords:
Chronic kidney disease
Cardiorenal syndrome
Heart failure with reduced ejection fraction
Heart failure with preserved ejection fraction
Pulmonary hypertension

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%) respectively. 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.

© 2016 Published by Elsevier B.V. on behalf of Cardiological Society of India. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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.

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. HFrEF was present in 59 (73.75%) patients. Total prevalence of left heart failure was 61 (76.25%) patients, with HFrEF 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%) |
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 2

| 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

| 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

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

Table 5

| 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 | 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 grades | PASP (mm Hg) | Stage of CKD | Total |
|-----------|--------------|--------------|-------|
| 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 feature          | LV failure (n=80) | p value |
|---------------------------|------------------|---------|
|                          | Present (n=61)   | Absent (n=19) |
| Breathlessness            | 59               | 9       | 0.0001* |
| Fatigue                   | 40               | 8       | 0.106   |
| Chest pain                | 10               | 1       | 0.444   |
| Pedal edema               | 56               | 9       | 0.0001* |
| Pleural effusion          | 14               | 3       | 0.749   |
| Pulmonary edema           | 35               | 2       | 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 (n=80) | p value |
|----------------------|------------------|---------|
|                      | Present (n=61)   | Absent (n=19) |
| P pulmonale          | 1                | 0       | 1       |
| Left ventricle strain| 50               | 2       | 52      | 0.014   |
| Ischemic heart disease*| 4                | 0       | 4       | 0.56    |
| Right ventricular strain| 13              | 0       | 13      | 0.030   |
| Complete heart block  | 2                | 0       | 2       | 1       |

* 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, 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 dimethylarginine, 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 m². 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.

| Characteristic              | LV failure (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 | 0.849   |
| 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 H2O)              | 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   |
| Hemodialysis duration (weeks) | 28.87 ± 46.80   | 12.5 ± 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.
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. Volume overload is attributed to sodium and water retention, anemia, and the presence of an arteriovenous fistula in patients with ESRD. 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 cardiotoxic steroids. 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.

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. These changes also explain their predisposition to arrhythmias and sudden death, which account for more than half of the cardiovascular mortality in them. 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.

The high prevalence of LV hypertrophy on echocardiography implies that these patients require detailed cardiovascular evaluation and treatment of CKD which is often overlooked. All these cardiovascular manifestations independently contribute to adverse outcome in these patients.

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 B12 and folate due to malabsorption and anorexia, impaired coagulation and platelet function due to uremia, hyperparathyroidism, bone marrow fibrosis, and chronic inflammation. In consistent with these studies, PH was present in 43.75% of the patients in our study.

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.

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

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. These changes also explain their predisposition to arrhythmias and sudden death, which account for more than half of the cardiovascular mortality in them. 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.

The high prevalence of LV hypertrophy on echocardiography implies that these patients require detailed cardiovascular evaluation and treatment of CKD which is often overlooked. All these cardiovascular manifestations independently contribute to adverse outcome in these patients.

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 B12 and folate due to malabsorption and anorexia, impaired coagulation and platelet function due to uremia, hyperparathyroidism, bone marrow fibrosis, and chronic inflammation. In consistent with these studies, PH was present in 43.75% of the patients in our study.

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.

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

The high prevalence of LV hypertrophy on echocardiography implies that these patients require detailed cardiovascular evaluation and treatment of CKD which is often overlooked. All these cardiovascular manifestations independently contribute to adverse outcome in these patients.

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 B12 and folate due to malabsorption and anorexia, impaired coagulation and platelet function due to uremia, hyperparathyroidism, bone marrow fibrosis, and chronic inflammation. In consistent with these studies, PH was present in 43.75% of the patients in our study.

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.
References

1. Centers for Disease Control and Prevention. National chronic kidney disease fact sheet: general information and national estimates on chronic kidney disease in the United States. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2014.

2. Centers for Disease Control and Prevention. Leading causes of death. 2013.

3. Modi G, Jha V. Incidence of ESRD in India. Kidney Int. 2011;79:573.

4. Pateinakis P, Papagianni A. Cardiorenal syndrome type 4—cardiovascular disease in patients with chronic kidney disease: epidemiology, pathogenesis, and management. Int J Nephrol. 2011;2011:938651. http://dx.doi.org/10.4061/2011/938651.

5. Ronco C, McCullough P, Anker SD, et al. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J. 2010;31:703–711.

6. House AA, Anand A, Bellomo R, et al. Definition and classification of Cardio-Renal Syndromes: workshop statements from the 7th ADQI Consensus Conference. Nephrol Dial Transplant. 2010;25:1416–1420.

7. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164(March (6)):659–663.

8. Stehouwer CDA, Smulders YM. Microalbuminuria and risk for cardiovascular disease: analysis of potential mechanisms. JASN. 2006;17(8):2106–2111.

9. Ninomiya T, Perkovic V, De Galan BE, et al. Albuminuria, and risk of cardiovascular and all-cause mortality in the US population with chronic kidney disease: epidemiology, pathogenesis, and management. Am J Kidney Dis. 2006;47(5):790–797.

10. Astor BC, Hallan SI, Miller ER, Yeung E, Coresh J. Glomerular filtration rate, albuminuria, and cardiovascular and all-cause mortality in the US population. Am J Epidemiol. 2008;167(10):1226–1234.

11. Weber-Mzell D, Kotanko P, Schumacher M, et al. Coronary anatomy predicts presence or absence of renal artery stenosis: a prospective study in patients undergoing cardiac catheterization for suspected coronary artery disease. Eur Heart J. 2002;23(21):1684–1691.

12. McCullough PA. Why is chronic kidney disease the “spoiler” for cardiovascular disease: analysis of potential mechanisms. JASN. 2006;17(8):2106–2111.

13. Kasiske BL. The kidney in cardiovascular disease. How soon does start? Nephrol Dial Transplant. 2014;29:2069–2074.

14. Eman K, Wanner C, Ritz E. Cross-talk between the kidney and the cardiovascular system. JASN. 2006;17(8):2112–2119.

15. Loui MA, Memoli B, Contaldi C, et al. Myocardial fibrosis and diastolic dysfunction in patients on chronic haemodialysis. Nephrol Dial Transplant. 2010;25(6):1950–1954.

16. Herzog CA, Mangrum JM, Passman R. Sudden cardiac death and dialysis patients. Semin Dial. 2008;21(4):300–307.

17. Mizobuchi M, Towler D, Slatopolsky E. Vascular calcification: the killer of patients with chronic kidney disease. JASN. 2009;20(7):1453–1464.

18. McCullough PA, Agarwal M, Agarwal V. Risks of coronary artery calcification in chronic kidney disease: do the same rules apply? Nephrology. 2009;14(4):428–436.

19. Blacher J, Guerin AP, Pannier B, et al. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension. 2001;38(4):938–942.

20. Ohya Y, Iseki K, Iseki C, et al. Increased pulse wave velocity is associated with low creatinine clearance and proteinuria in a screened cohort. Am J Kidney Dis. 2006;47(5):790–797.

21. Debnath A, Chaudhury SR, Chaturvedi AN, et al. Echocardiographic assessment of left ventricular systolic dysfunction in chronic kidney disease patients of a rural tertiary medical care centre in West Bengal. IOSR-JDMS. 2014;13(1):69–73.

22. Zoccali C, Benedetto FA, Mallamaci F, et al. Prognostic value of echocardiographic indicators of left ventricular systolic function in asymptomatic dialysis patients. J Am Soc Nephrol. 2004;15:1029–1037.

23. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561–1566.

24. Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995;47:186–192.

25. 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.

26. Paoletti E, Bellino D, Cassotopa P, et al. Left ventricular hypertrophy in non-diabetic peritoneal dialysis. CKD. Am J Kidney Dis. 2005;46:320–327.

27. Yi Ma, Xiaohua S, Fei L, Sabag A, et al. Pulmonary hypertension in patients with end-stage renal disease. Chest. 2003;123:1577–1582.

28. Andrew M, Meghan E, Richard N. Pulmonary hypertension in patients with chronic end-stage kidney disease. Kidney Int. 2013;84:682–692.

29. Rolingano D, Rastelli S, Agarwal R, et al. Pulmonary hypertension in CKD. J Am Soc Nephrol. 2013;61(4):612–622.

30. Kumbar L, Fein PA, Rafiq MA, et al. Pulmonary hypertension in peritoneal dialysis patients. Adv Perit Dial. 2007;23:127–131.

31. Fabbian F, Cantelli S, Molino C, et al. Pulmonary hypertension in dialysis patients: a cross-sectional Italian study. Int J Nephrol. 2011283475.

32. Babitt J, Lin HY. Mechanisms of Anemia in CKD. JASN. 2012;23(October):1631–1634.

33. Arzt AS, Cleton-B. Prevalence of anemia in the nursing home: contribution of chronic kidney disease. J Am Geriatr Soc. 2007;(October (10)):1566–1570.